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BULLETIN

OF

THE NEW YORK ACADEMY OF MEDICINE

INCORPORATED 1851

JULY, 1934

PUBLISHED MONTHLY BY

THE NEW YORK ACADEMY OF MEDICINE

2 East 103 Street

New York, N. Y.

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ANNUAL GRADUATE FORTNIGHT
"DISORDERS OF METABOLISM"
October 23 to November 3, 1933

CLINICAL AND BIOLOGIC CONSIDERATIONS OF OBESITY AND CERTAIN ALLIED CONDITIONS*

ALBERT A. EPSTEIN

Obesity is a commonplace condition. Fashion makes it a frequent topic of conversation, and the attention of the physician is directed to it more often by a patient's desire to reduce for aesthetic reasons, rather than for reasons of health. Our interest in the subject, however, should be based upon the fact that certain dangers are inherent in obesity. The susceptibility of obese individuals to infectious diseases, to diabetes, and to the degenerative diseases of the cardio-vascular system, as well as the higher mortality from all causes in the obese as compared to the non-obese, are well known facts, and are all questions which render the subject worthy of the most serious consideration. The approach to the subject, however, is extremely difficult because the literature, both professional and lay, is as you know replete with information both relevant and irrelevant.

*Delivered October 31, 1933.

Our scientific knowledge of obesity may be said to be in a state of flux, and by no means final. Obesity constitutes a problem in which nearly all phases of metabolism are represented, and in which the specific physiology of every organ and tissue in the body is somehow concerned.

Properly defined, obesity signifies an increase in body weight in excess of the limitations of skeletal and physiologic requirement, due to the deposition of fat. Common usage has made the term synonymous with adiposity, lipomatosis, and in fact all forms of corpulency irrespective of their nature or origin. This broad use of the term obesity is not accidental; it is the result of the difficulties which attend all attempts at sharp clinical differentiation.

It is customary to divide all cases of obesity into two general groups: the exogenous and the endogenous. The term exogenous is applied to those cases in which the obesity is due either to overeating or lack of exercise; a purely mechanistic conception in which the principle of the conservation of energy is believed to be operative. The term endogenous is applied to cases in which the obesity cannot be ascribed to overfeeding or underexercise alone, but in which an additional factor is concerned. Cases in this group often present evidence of glandular dysfunction, hence the term endocrine obesity has been introduced. Endocrine is however, a specific term and should be applied only to those cases in which a definite glandular etiology can be established. The designation of obesity as exogenous or endogenous is often merely a matter of point of view, based upon the therapeutic experience of the observer.

An increasing number of investigators are of the opinion that, with but a few exceptions, obesity is the result of alimentary maladjustment in which food intake exceeds energy output, and that this process may be reversed by proper dietary restrictions. There are still others, however, who hold to the view that tissue preparedness, conditioned by constitutional and hereditary factors, is essential for the deposition of fat.

While fat may be the chief substance deposited in the tissues, most observers agree that not all cases of corpulency are necessarily of that origin. Other substances such as mucin may be deposited, or even the overdevelopment of structures other than the adipose tissue may contribute to the final result.

For a proper understanding of the subject, the following questions must be considered: 1. What is the normal weight of an individual and how is it maintained at a constant level? 2. If stability in weight is the resultant of a mechanism which functions constantly and which adjusts food intake to energy output, then what is it that initiates a departure from the normal which permits an increment in weight? 3. Does tissue activity alone control and regulate the demand for food, and are hunger and appetite the result of that demand? 4. How are the various nutrients constantly present in the body utilized, and what relation do they bear to oxidative processes and tissue activity? 5. What role do the endocrine glands play in the regulation of metabolic processes and tissue activity, and how does disease or dysfunction of one or another of these glands affect this regulation?

The first question to be considered is the normal weight of an individual which is commensurate with his skeletal and physiologic requirements. For this there is no absolute standard. Certain values have been arrived at from a comparison of the weights of large numbers of presumably normal persons and the law of averages applied. Such a method permits a variation of at least 10 per cent in either direction. Hence, while the weights given in standard tables are very useful, discretion must be used in their clinical application. Experience teaches that small excesses in weight, or the reverse, may be disregarded in the otherwise healthy individual.

What is the mechanism then which maintains the weight of an individual at normal? This is the key to the solution of the whole problem of obesity. Food is the source from which the energy developed by the body is derived. Since

the law of the conservation of energy still holds good, it is necessary to conclude that the maintenance of a constant weight represents the resultant of an adjustment between the potential energy supplied by food and the active or kinetic energy expended by the body. Normally there is an automatic regulation of the output of energy and the intake of food. An adult after having attained an optimum weight, that is a medium average of nutrition, adjusts himself to a definite amount of food that constitutes for him the so-called maintenance diet which deviates upward and downward from the average according to the varying demands created by a varying amount of physical labor performed. Of course, the exact amount of food that corresponds to the consumption of energy for each day is not introduced during each 24 hour period. These differences become so completely equalized by small increases and decreases, that many persons maintain their weight at a fixed level for a period of years. This finely adjusted normal regulatory mechanism is occasionally disturbed, sometimes forcibly, but more frequently by the accumulation of slight influences producing a large effect, as for example, when the expenditure of energy remains constant, and the food intake is increased but slightly. Small excesses of food over the usual amount are sufficient to upset this balance. Assuming that the daily surplus amounts, on an average, to 200 calories, which is contained in 1½ glasses of milk, an ounce of butter, ¼ pound of meat, or 2 ounces of bread, let us note the result.

After deduction of the incidental expenditures of energy, such as that attributable to the specific dynamic action of the food itself, these additions to the diet can produce daily additions of about 20 gms. of fat, and in a year about 16 pounds in weight. As fat is always deposited in conjunction with other substances, particularly water, the gain in weight may reach a sum total of 22-25 pounds in the course of a year.

In this connection it may be stated, that alcohol may supply the excess just referred to. Alcoholic beverages

are conspicuous for their tendency to cause weight increase; they are not used in place of other articles of food, but are generally added to a diet that is in itself already sufficient to maintain nutrition. Under these circumstances the complete caloric value of the alcohol becomes utilized as a means of fattening. This is readily appreciated when it is realized that one ounce of alcohol protects approximately its equivalent in weight of fat from combustion which may remain stored in the body.

As a corollary to the preceding, increase in weight may result when food intake remains the same but energy consumption is decreased. The desire for food and the actual intake of food under normal conditions, correspond to the increase or decrease of energy output. Occasionally this regulatory adjustment is interrupted, particularly when individuals who have been accustomed to strenuous labor, or much exercise, suddenly change their occupation or habits, and begin to lead a less active life. In men this frequently occurs towards the fifth decade of life, or somewhat later, in women about ten years earlier. While the habits in regard to the amount of food consumed may remain the same as in previous years, less energy is expended, so that what was formerly an adequate diet, now becomes a surplus one. These factors may produce either slowly or rapidly an increase in the fat deposits of the body. Of course external circumstances, of the character described above, are not the only causes that may lead to a more sedentary method of life, disease for instance, may cause such a change in habits, especially disturbances of circulation, diseases of the respiratory apparatus, of the nervous system or the organs of locomotion. While physical activity is a potential element in the constancy of weight, it must not be assumed that it is the only source of energy responsible for this balance. Energy output represents the summation of three metabolic processes, a disturbance in any one of which may contribute to an imbalance between the intake and output of energy. They are: 1. the basal metabolic rate, representing the sum of

all the oxidative processes of the body when completely at rest; 2. the accessory oxidative processes due to the specific dynamic action of food; and 3. the accelerated metabolism or oxidative processes due to work or exercise.

The applicability of the principle of the conservation of energy to the maintenance of weight equilibrium cannot be denied, but its operation is not always apparent, nor can the automaticity of the operation be so easily explained. For there are many persons who eat much without ever showing any increment in weight, while others gain weight with remarkable facility. Moreover another circumstance which is not entirely in accord with the view that weight equilibrium is the simple result of a balance between food intake and the amount of energy liberated, is the fact that reduction in food intake below energy output does not always yield uniform results. It is this incompatibility in the mechanistic concept of obesity which presents the greatest difficulty. This view has caused much speculation and has given rise to a number of different theories. It would take us too far afield to discuss them at length; yet they cannot be dismissed without some consideration.

The dependence of food intake on appetite and its relation to tissue activity is a very complex problem; for example, demand for food can increase without increase in tissue activity and is well illustrated in lesions of the brain, particularly those in the hypothalamic region. Deprivation of an essential nutrient, as in diabetes mellitus, may cause an increase in demand for food without augmentation of tissue activity. Increase in tissue activity may occur without increased demand for food, as in hyperthyroidism, fevers, and cachectic states.

Certain investigators claim to have demonstrated the occurrence of a "negative phase" or temporary depression in metabolism after light exercise and following the ingestion of food. They regard this as important in the maintenance of weight equilibrium. A confirmation of these findings would be extremely helpful in understanding this problem.

Recently the view has been advanced that weight stability is of very much the same nature as temperature stability, and that the determining factor resides within the brain. This view is based upon experimental and clinical evidence in which it was noted that injury or disease of the hypothalamic region, as already alluded to, is followed, often very promptly by excessive increase in weight. Stability in weight is not necessarily characteristic of the individual of normal weight; such stability is often present for long periods of time both in the obese as well as in the undernourished individual.

None of the foregoing hypotheses adequately explains the mechanism which maintains the weight of an individual in equilibrium. This being the case, it is self evident that any attempt to elucidate the origin of obesity is even more difficult.

Obesity is so obviously a departure from the normal state that it is natural to seek its explanation in deviations of metabolism from the normal. Thus, reduced activity of the tissues, as evidenced by lowered metabolic rate; reduced kinetic response of the tissues to food, i.e. refractoriness to the specific dynamic action of food; increased formation of fats from carbohydrates; improper oxidation of fats, etc. have been regarded as primary or contributory causes of obesity. But a careful analysis of the available information on these questions fails to reveal any dependable evidence indicating that any or all of the metabolic processes just mentioned are definitely responsible for the development of obesity. This may be in part due to the fact that the bulk of our information is derived from observations on individuals already obese; the metabolic observations noted are irregular, inconstant, or often too trifling to be conclusive. A characteristic of the living organism is its adaptability to changed conditions. Obesity is a condition which is usually slow in development, so that the absence of any evidence of a metabolic disturbance in an obese individual is no indication that such a disturbance does not exist at the outset. The final state of the meta-

bolic processes as ascertained may represent the end result of a long series of adjustments by means of which a balance has been established.

Newburgh has shown that in obese patients the energy expenditure is less than the caloric intake, and that a positive energy balance exists. He has also shown quite definitely that if the energy intake be reduced below the output, these patients will lose weight. This is in conformity with the original definition of obesity, but does not explain why obese patients consume more food than they require to maintain their established weight, or why their energy expenditure on a given caloric intake is less than that of normal people. This is a strictly mechanistic viewpoint which explains the ultimate effects of overfeeding and accounts for the so-called exogenous obesity, but gives no hint as to the initial cause of the increased consumption of food and its consequences.

An answer to this query is to be found in the conclusions recently arrived at by Strang and Evans, who maintain that the active tissues of the body are chiefly concerned in the elaboration of the metabolic processes and that adipose tissue itself is relatively inactive. Hence, they conclude that all computations should be based upon the mass of active tissue in the body. If this manner of computation is employed, it is found that the metabolism of active tissue must be considerably above normal in order to maintain metabolism at the estimated level; whereas the metabolic rate based upon surface area may be normal, or less often subnormal in the obese. From their results, it would appear that tissue activity in obesity is not reduced but actually increased.

The question arising at this point is: What is the mechanism which permits obese persons to remain for a long time on a positive energy balance; why do they continuously exceed their caloric necessity? Attention should be directed to deviations in the normal relationship between appetite on the one hand, and energy expenditure on

the other. When this relationship is in perfect adjustment, as it is normally, no obesity develops; but, when appetite exceeds energy requirement obesity appears.

There is no evidence to prove that increased appetite is the primary cause of obesity. It is conceivable that another factor, "The undeterminable tendency to obesity", may in itself be responsible for the increased appetite. Putnam, Benedict and Teel have shown experimentally that there is a relationship between growth and appetite, and if we compare obesity to growth in general, it is fair to admit that appetite is the result and not the cause of the process.

The concept of the endogenous nature of obesity does not deny the principle of the conservation of energy, it goes a step further and attempts to explain the mechanism on the basis of an hereditary or constitutional predisposition. The terms "hereditary and constitutional" as related to obesity do not lend themselves to specific definition, and may in the last analysis signify a cryptic disorder of the endocrine glands. Increased tissue avidity or lipophilia appears as a corollary to the constitutional concept of obesity. The effects of central disturbances on body weight, as well as the selective and characteristic distribution of fat in thyroidal, gonadal and pituitary dysfunctions lend support to this view. Moreover, under certain conditions, the general body fat may disappear without affecting the localized deposits.

Contrary to the view presented earlier in this discussion, some investigators are of the opinion that the position of adipose tissue in the animal economy is not that of a passive structure, but is the seat often of very active changes, affecting specifically the relations between carbohydrate and fat metabolism. It is believed that fat cells are capable of converting carbohydrates into fat. The presence of glycogen in these cells, under certain conditions, is interpreted as indicating such a process. It has also been suggested that nerve as well as hormonal influences play a part in this process.

To summarize, the deposition of fat in varying degree is present in all types of obesity, the only distinction being the rate of deposition or its distribution. In exogenous or generalized obesity an increase of adipose tissue usually occurs in the normal depots.

Considered practically, therefore, the first problem which concerns the physician is that dealing with the accumulation of fat.

In the early stages of life, a certain degree of obesity is regarded as physiologic and the excess weight represents a reserve of material and a potential source of energy, while the obesity of the latter period of life is regarded as unphysiologic, because of the many true and alleged ill effects which it may produce. Normally, adipose tissue is an important element in the structure of the body and constitutes approximately 22 per cent of its weight. Thus obesity may represent, on the one hand, a temporary normal expedient and on the other a process or condition which is probably physiologic in its origin and pathologic in its consequences.

Fortunately, unless and until the obesity causes definite pathologic changes, the conditions leading up to it are reversible, and with a reduction in food intake over the energy output, fat is ultimately mobilized from its depots and utilized as body fuel. This forms the principle upon which the modern treatment of obesity is largely based. Recent investigations support more and more the mechanistic concept of obesity and all therapeutic procedures employed rely upon this concept.

The distribution of body fat may be very widespread and some vital organs may become affected. In universal or general obesity, the magnitude and distribution of fat is not uniform throughout the body. Some localities acquire increments earlier than others and possess the capacity of storing fat to a greater degree. Fat, sometimes in enormous quantities, is lodged in the subcutaneous and intramuscular tissues, the bone marrow, the mesentery, the omentum, and retroperitoneal tissue, the epicardium, the

tissues about the kidneys, and the orbit. In extremely obese persons the fat after filling these places to their utmost, seems to overflow into unexpected localities, such as the wall of the heart and also beneath the endocardium; it pushes apart the lobules of the pancreas and spreads around to the free surface of the intestines. This distribution is characteristic of all cases of alimentary obesity, but it does not apply to those obesities in which hormonal or endocrine influences play a part. In these cases the normal depots may remain unaffected, while unusual locations are chosen for the deposition of fat.

As previously pointed out, the excess weight in the obese person is not always due to fat alone. Thus the outward manifestations and consistency of the panniculus show striking variations, such as texture, mobility and attachment of the skin to the underlying tissues. This can be readily appreciated when the character of the obesity usually encountered in men is contrasted with that of women, except in those women under forty in whom the obesity is due to deliberate overeating.

In the matter of the obesities now to be considered, which are due to failure on the part of one or another endocrine gland, there are certain general principles to be borne in mind. The first is that many an obesity of primary alimentary origin becomes complicated by elements of endocrine failure. In very pronounced cases of general obesity, evidences of thyroid inadequacy are often present. When particularly outspoken, the case is liable to be regarded and treated as one of hypothyroidism or myxedema, not only with indifferent success, but occasionally with the provocation of untoward symptoms. It is also necessary to remember that an endocrine obesity nearly always denotes failure, relative at least, of more than one gland, and that it is in fact very often a pluriglandular rather than a monoglandular syndrome.

The thyroid type of obesity is too well known to require any detailed description. Its development is proportionate to the degree of thyroid deficiency. It constitutes in

reality a pseudo-obesity; the deposition of fat is incidental and the corpulency is due to the deposition of mucinous or myxedematous tissue, with a special predilection for certain localities.

Dysfunction or cessation of the endocrine activity of the procreative glands is accompanied by the development of obesity, both in the female and the male. The climacterium in the female, whether artificial or spontaneous, is followed as a rule by a corpulency which is not distinguishable from that which accompanies hypothyroid states, and may in many instances be accompanied by an actual hypofunction of that gland. The metabolic accompaniments of a true hypothyroidism are not frequently demonstrable in this type of obesity.

The type of obesity due to interference with the testicular hormone varies with the cause. It is necessary to distinguish between the results of a surgical castration, and the effects of lack of development or atrophy of the testicles. Differences in the clinical manifestations depend upon the stage in sex development in which castration occurs, that is, before or after puberty.

I shall not enter into a detailed description of these various conditions, as they are amply described in most textbooks. Suffice it to say that in pathologic hypogonadism the close approach of the individual to the feminine type serves to implicate these glands.

The chief difficulty in the differential diagnosis of endocrine obesities lies between the type due to gonadal insufficiency and that which results from deficiency of one or both lobes of the pituitary. Perhaps the most important differential point is that in strictly gonadal insufficiency, obesity is a late manifestation, whereas in the pituitary inadequacy it is more likely to appear early. Differences in skeletal development may be of assistance in establishing the true origin of the associated obesity. Generally speaking obesity of pituitary origin is a girdle obesity; the adipose tissue is deposited chiefly in the area which is

bounded above by the diaphragm and below by the knee. When there is a conspicuous deposit of fat in any area outside this region, it is almost always due either to alimentary causes or to a concomitant defect in some other gland; the glands most commonly involved being the gonads.

Unlike the exogenous type of obesity, that due to endocrine disturbance is sometimes accompanied by changes in the metabolic reactions. Those due to hypothyroidism, particularly those of severe degree, may show definite reduction in the basal metabolic rate, and a disposition to increases in the lipoid content of the blood, a diagnostic point of considerable importance. Increase in carbohydrate tolerance may also be observed. Those of pituitary origin show little or no change in the metabolic rate, slight if any increase in lipoid content of the blood, but occasionally a decided decrease in carbohydrate tolerance; while those of gonadal origin may show no other abnormalities than a moderate or considerable increase in the lipoid content of the blood. Again attention must be called to the fact that, in most instances, the endocrine type of obesity is rarely due to a decrease or cessation of function in one gland alone, so that the distinguishable features in respect to the metabolic aberrations just mentioned, are not always clearly defined or constant.

In all the aforesaid, emphasis has been laid particularly upon the causes of overweight; first and most important is fat; then the non-adipose tissue such as mucinous substance and the like. There is, however, one other substance which contributes to obesity in a large measure, namely water. The association of water retention with obesity is so constant that its occurrence cannot be regarded as casual or accidental. I am inclined to the view that the retention of water is a necessary concomitant of fat deposition. The relation which they bear to one another is regulated by the biophysical and biochemical state of the colloids of the blood and the tissues; an excellent example of this regulation is to be found in nephrosis. To put it in a word, obesity represents a lipedema, a migration and

deposition of water and fat to the various tissues of the body, and can arise from causes originating from within, or may be induced by extraneous factors. This concept aids in elucidating a number of questions. Time will not permit me to discuss the evidence. Suffice it to say that in devising therapeutic procedures and in analyzing their effects, water metabolism must be taken into strict account.

Mineral salts are closely associated with water retention. Gamble, Ross and Tisdale have demonstrated certain facts regarding water and mineral metabolism, indicating that the sum and total of chemical bases is important in maintaining the structural integrity of the body fluid. They computed the weight of water lost during fasting in terms of fixed bases, and have demonstrated that losses up to 62 per cent of body weight may be due to water. There are many cases of obesity in which retention of water and salt may be wholly unsuspected. These patients when dieted strictly may be greatly undernourished yet suffer no apparent loss of weight because of water storage. Von Noorden in 1910 already warned about the importance of water and salt retention in the treatment of obesity. Zondek designated such patients as the "salt-water-obesity type"; Bauer speaks of them as cases of "hydro-lipomatosis". The water balance in obese persons has been accurately studied by Newburgh and his associates; they have shown that obese individuals kept on a strict metabolic regime may hold, or even gain weight due to water retention. Certain complicating factors common to obesity must be reckoned with when interpreting the relation of overweight to retention of fluid; chief amongst these is circulatory inadequacy and cardio-vascular disease.

It is quite obvious that whatever the ultimate mechanism underlying fat deposition or water retention may be, in applying therapeutic procedures to obesity, these facts must be borne in mind and seriously considered. Frequently success or failure depends upon the proper interpretation of these conditions.

In discussing the complications of obesity, we must distinguish two sets of conditions, namely, those in which complications occur in an already established obesity, and those in which obesity is a sequel to other diseases. In the first category belong cardio-vascular disturbances, diabetes, biliary diseases, gout and infections; in the second, orthopedic conditions, pulmonary tuberculosis, and primary cardiac disease; in other words, conditions in which sedentarism plays an important part.

It is common knowledge that obesity carries with it certain potential dangers which sooner or later manifest themselves clinically. Firstly, excess of adipose tissue frequently constitutes a mental and physical handicap, and tends to promote the very conditions which cause obesity and make it progressive. Secondly, and probably the most important, is the problem of cardio-vascular disturbances. As a result of the deposition of fat in the tissues, some of the smaller blood vessels must sooner or later yield to the greater pressure of the fat and compensatory circulation must be established. Failing this, the increased peripheral resistance may lead to an increased blood pressure. Because of this, increases in blood pressure, particularly in the earlier stages of obesity are not uncommon. On the other hand, in many cases of obesity of long standing, a low or subnormal pressure is encountered, unless still other conditions complicate the picture. The cause of the fall in blood pressure may in part be due to the establishment of compensatory circulation, which relieves the load in the peripheral circulation; or the pressure may fall because of cardiac insufficiency. Peable states that the mortality from heart disease in the obese is two and one-half times as great as in persons of normal weight. This effect upon the heart is in all probability the result of a number of causes which are operative in obesity, namely: 1. increase in peripheral resistance as mentioned above; 2. infiltration of the heart muscle itself, lessening its contractile power; 3. as Strang and Evans have shown, that while the basal meta-

bolic rate of the obese as measured in terms of surface area, is usually normal, the oxidative processes in the active tissues of the body are markedly increased; a circumstance in which the heart is greatly concerned. This fact gains particular significance from the recent work of Blumgart, who found that reduction in the oxidative processes of the body, i.e. diminishing the basal metabolic rate by ablation of the thyroid, serves to reduce the cardiac load and spares the heart when it is greatly embarrassed and decompensated; 4. water retention, which is so constant a phenomenon in obesity, may be a cause as well as a sequence of cardiac insufficiency. Clinical observations indicate that the simple removal of water from the body exerts a beneficial effect upon the heart and circulatory system in cardiac failure, and from this we may infer that water retention occurring in obesity plays an important part in embarrassing the heart and circulatory system. It is probably safe to say that many of the beneficial effects of reducing procedures, so far as the heart and the circulatory system are concerned, are in a large measure to be ascribed to the incidental removal of much stored water.

Another very important complication of obesity is diabetes. Many clinicians are of the opinion that obesity bears a direct etiologic relation to diabetes. This connection is so firmly established that to contradict it would seem like heresy, and yet I feel that the data can bear closer scrutiny. The association of obesity with diabetes is indeed common. Both diabetes and obesity frequently bear the character of familial diseases or conditions, the importance of which cannot be ignored in statistical deductions. When a familial or hereditary factor relative to diabetes exists in any individual, the advent or coexistence of obesity may conceivably hasten or induce diabetes; but, whether a diabetes would develop as a direct sequel of obesity, in a person free from hereditary taints, is very problematic. Obesity may bear a pathogenic relationship to diabetes, but whether it is the direct cause of it is still an open question.

Overfeeding is in most instances the direct cause of obesity. Overfeeding may play a part in the exhaustion of the vital organs, amongst others, the pancreas and the liver, and may lead to the development of diabetes. But whether or not an obesity once established is capable of producing these functional effects upon the vital organs is by no means proven. It is reasonable, however, to suppose that the avoidance of overfeeding may obviate not only the obesity but incidentally a possible diabetes.

When we consider the active participation of the liver in the intermediate metabolism of fat, the development of biliary diseases in obesity is readily comprehensible. Appropriate feeding experiments show that the fats entering the body pass through the liver, become modified (hydrogenated) there, and then either undergo utilization or are deposited in the adipose tissues. On the other hand, in fasting or starvation, the fats are mobilized from their depots, carried to the liver and thence transported to various points in the body for utilization. Thus the liver is the central receiving and transmitting station both for exogenous and endogenous fats. In obesity the conditions appear to be particularly favorable for the development of biliary disorders. The incidence of cholelithiasis and other biliary diseases is, however, greater in women than in men, so that disorders of fat metabolism cannot alone be incriminated for the development of biliary disease, and factors incidental to the female sex must play a contributory if not provocative role. One fact in particular is worth mentioning in this connection, namely, that the occurrence or the recurrence of biliary disease is occasionally encountered in the course of reduction treatment for obesity. This too, is more frequently encountered in women than in men, and particularly when a rapid method of reduction is employed.

When gout was a more common malady than it is today, obesity was often associated with it, and prevailing opinion ascribed to the obesity an etiologic importance in the development of gout. While gout is by no means extinct, its

incidence, particularly in the arthritic form is rare. Atypical cases, in which a uric acid diathesis can be definitely established, are still encountered with some frequency, but its causal relation to obesity is by no means evident. There can be no doubt, however, that dietary indiscretions play an important part in the production both of gout and obesity, but certain other factors, usually adjudged to be constitutional, appear in the clinical picture.

It is also stated that obese individuals are particularly prone to infections, chief of which is pneumonia. This too is something which my own experience would lead me to question very seriously.

While obesity itself may promote sedentarism and thus aggravate pre-existing conditions such as orthopedic diseases, rheumatic states, cardiac disturbances, pulmonary tuberculosis, etc., it is plain also that such conditions require reduction of activity and favor sedentarism, and thus lay the foundation for the development of obesity. These conditions should, properly speaking, not be regarded as complications of obesity but as diseases frequently complicated by obesity.

Much or little can be said concerning the prognosis of obesity. We are still too uncertain as to whether obesity represents a disease, or merely an exaggerated physiologic condition. It may develop as a sequel to disease or may in itself be the precursor of definite pathologic developments. In either instance the outcome depends primarily upon the associated disease. The most that can be said is that obesity lessens the chances for recovery in any condition and must be considered as a serious element in every prognostic appraisal. Existing per se, and uncomplicated by other conditions, obesity offers no rules for guidance as to prognosis.

A great variety of methods have been introduced in the treatment of obesity, some of them on reasonable grounds and others not. Before discussing these methods, it is

well to consider first, the indications; how the degree of obesity can be appraised, and how far one should proceed. From the standpoint of indications, men and women present somewhat different problems. Reduction methods are often instituted, promoted by fashion or vanity, and not by the exigencies of hygiene or good health. In men, as well as in women, the indications for reduction should not be gauged exclusively by the accepted standards of normality in weight. Good health should be the first consideration. The presence of hereditary or familial trends in the history of pathologic manifestations as well as the age of the patient should all weigh in the final objective.

Generally speaking the older the individual, the less desirable does reduction of weight become, particularly if the obesity is not extreme, and if no clinical manifestations exist which would be benefited by loss of weight. It is only when pathologic developments occur or, when the weight itself is a hindrance in the exercise of normal activities and functions, that reduction should be considered.

It has been pointed out that vital statistics ascribe a higher mortality from all causes to the obese, but definite information is still lacking as to whether or not reduction of obese individuals is effective in actually prolonging their life beyond the usual period of expectancy. A close approximation of the ideal weight of an individual is obtained from standard tables. It has been observed in the study of such tabulations that a certain fairly constant numerical relationship exists between the skeletal dimensions and the weight factor; this has led to the evolution of a number of formulae for the computation of the ideal weight. The simplest of these is the one suggested by Moritz; the height of an individual is determined in centimeters. The number of centimeters over and above 100 is translated into kilograms and approximates the ideal weight. This formula has certain limitations, but it is of sufficient accuracy for clinical application. A variation of 10 per cent either way is regarded as normal, but surpluses greater than 10 per cent must be regarded as constituting obesity.

Efforts to control obesity date back many years, but the treatment of obesity has not received the earnest consideration from the profession that it deserves. Lukewarm interest and relative indifference have always characterized the doctor's attitude toward the subject; consequently the treatment of obesity has become grossly vulgarized, so that ultimately most obese individuals, particularly women, become the prey of commercial and other unscrupulous exploitation. Each day brings forth some new method of treatment or new device for reduction of weight, or at least an old one in a new guise.

Attention has been drawn to the pathogenic potentialities of obesity, and it is on their account that obesity becomes a pressing problem in preventive and palliative medicine. We have defined obesity as a condition in which an increment in weight follows when food intake exceeds energy output. It has also been indicated that in most instances the process is reversible. The main object of all forms of treatment is, therefore, a reversal of the conditions which lead to obesity, i.e., either a reduction in the food intake below the usual energy output, or an increase in energy output over the customary food intake, or both. When the customary intake of food becomes relatively excessive by reasons of decreased physical activity, then either the activity must be increased, or the diet reduced to the new level of nutritional requirement.

The most important problems in treatment relate, however to the already existing obesity. The question resolves itself into two phases: first, the treatment of those obese persons who show no complications and are otherwise well, and secondly those in whom obesity is a concomitant of some other disease.

The desired result in all these cases is a utilization of the stored fat as a source of energy. When the exogenous source of supply becomes reduced or depleted and the energy output remains the same, utilization of stored fat

occurs. Thus in the treatment of all forms of obesity reduction of diet is of primary importance. This is capable of great variation both qualitatively and quantitatively. The quantity of food restriction in any given case may be small or great and in some instances, may even border on starvation. The amount of restriction must vary according to the degree and the urgency of the result desired. Students of obesity generally agree that diets with a caloric value considerably below the basal requirement are the most efficacious in producing a prompt result. The degree of reduction sought is based, either on a foreknowledge of the weight of the patient prior to the development of the obesity, or the ideal weight for the individual, arrived at by means of the computations mentioned above. The time interval in which the reduction is to be obtained frequently determines the rigidity of the measures to be employed.

The caloric value of most modern reducing diets ranges between 800 and 1500 calories; some observers go considerably below this value, allowing only from 400-600 calories per day. However, the caloric value of the diet is not the only factor to be considered. The incidental and specific effects of the various food stuffs must be taken into account. Nitrogen loss does not ordinarily occur even after long periods of undernutrition, and tissue waste is readily guarded against by the administration of a basal amount of protein in the diet; about 0.6 to 1. gm. per kgm. body weight. On account of the specific dynamic action of protein which speeds up all the metabolic processes, diets containing much larger amounts of protein have been used with some success in reducing weight. On occasions a certain degree of debility may be experienced, particularly by young people during treatment; this is ascribable largely to the development of a moderate ketosis. A larger provision in carbohydrate intake serves to obviate this development. If marked undernutrition becomes necessary and treatment is protracted, provision must be made for an adequate supply of vitamine.

To describe a specific diet would be out of place, as a great variety of food combinations are possible. In any reduction diet it is important to give adequate amounts of protein, especially in the treatment of older individuals in whom physical deterioration must be guarded against.

Another very important factor in the loss of weight is the retention of water; it has been estimated that 1 gm. of carbohydrate causes from 3-5 gms. of water to be retained in the body, so that in order to effect the desired loss of weight, the carbohydrate intake must be reduced to a minimum. This may be accomplished by allowing approximately 0.8 gm. of carbohydrate per kgm. body weight. The combustion of the stored fat is accomplished by the generation of a large amount of water. It was pointed out earlier in the discussion that water retention constitutes a large part of the weight factor in obesity, and regardless of any theoretical considerations, it is a well known fact that obese people may fail to lose weight for a number of days even though they are undernourished. This is due to water retention. So that in observing the clinical effects of reducing diets, the influence of water must not be overlooked. It has been shown that under strictly controlled conditions, as much as 62 per cent of the loss of weight may be due to water. Mobilization of water is necessary for the successful reduction of weight. To that end a number of procedures have been devised, such as the administration of thyroid, salyrgan or neptal, calcium and other diuretics. The effect of these procedures is sometimes beneficial. It is important to remember in this connection, that the retention of water in obesity is frequently an expression of circulatory incompetency and attention must be given to that mechanism; it will be referred to again later. Experience teaches that when the outflow of water is not commensurate with the metabolic processes induced by undernutrition, the loss of weight is neither adequate nor enduring.

It was stated before that the treatment of obesity consists largely in a reversal of the conditions which cause

it; namely making the food intake less than the energy output, raising the energy output over the food intake, or both. We have already considered the first; now we come to the question of energy output. When the diet is properly adjusted the acceleration of the metabolic processes is accompanied by the combustion and utilization of body fat. Two methods are available to accomplish this. The first is increased physical activity through exercise, and the other is direct stimulation of the metabolic processes by medicinal means. Exercise increases the oxidative processes in the body, thereby accelerating energy output. Increased loss of water also takes place. But, exercise for the purpose of working off fat is merely a stimulant to the appetite. Unless accompanied by food restriction, its employment in the treatment of obesity is of questionable effectiveness.

Medicinal agents are frequently resorted to in the treatment of obesity. Chief amongst these is thyroid or thyroxin, thyractin, and recently dinitrophenol. Foreign proteins as milk or aolan have also been used. The purpose in the use of all of these is to increase tissue activity and hence the combustion of fat. Because of its effect upon metabolism, thyroid has always been regarded as a desirable adjuvant in the treatment of obesity. The popularity of all of these agents is based upon the misconception that they do away with the need for dietary restriction. But, experience teaches that barring those cases of obesity which are directly traceable to thyroid hypofunction, its usefulness is extremely limited. It is a remarkable fact, that whereas in the truly hypothyroid obesities, the amount of the hormone necessary to produce a definite effect is relatively small, in most other cases very large doses are necessary to produce a noteworthy effect. This is frequently achieved only at the expense of the patient's health, for the reason that in the obese person the thyroid is in all probability already subject to a definite functional strain.

To present the picture graphically, the obese individual may be conceived as possessing two bodies; an outer one consisting of adipose tissue which is relatively inactive, and an inner one made up of all the other tissues of the body which are metabolically active. We know that the basal metabolism is usually normal in obesity; that signifies that the inner body or the active tissues must work at a greater speed in order to maintain the metabolism at that level, than it does in the normal individual. The degree to which the metabolism of this inner body must rise is proportionate to the surface area due to the obesity. The increased rate of activity is presumably due to overactivity of the thyroid. From this it becomes obvious that the administration of thyroid in the treatment of obesity is a somewhat hazardous procedure, and as mentioned before, may be accompanied by toxic symptoms. I have found from experience that the untoward effects of thyroid therapy may be considerably diminished by the addition of small doses of iodine, and that much larger doses of thyroid can be tolerated if iodine is given at the same time. The other agents which I have mentioned such as the injection of foreign proteins, stimulate tissue activity through their pyrogenic properties. Dinitrophenol in small doses augments all the metabolic functions resulting in a steady loss of weight; in larger doses it produces a hyperpyrexia. However, it is too new a remedy to be used with any freedom and is capable of causing toxic manifestations. At best the results produced by pyrogenic agents are too brief to be of lasting value, unless a process of progressive tissue disintegration is induced by these substances.

It may be said therefore, that because of the physiologic strain which obesity throws on the organism, as evidenced by the high level of metabolism of the active tissues, thyroid extract and other agents which increase the total energy output, are generally contra-indicated. From observations on large numbers of obese individuals, it has been found that only very few, not over 2 per cent, do not lose

weight on diet alone. These patients cannot be differentiated from the others, either by history or physical examination; they may sometimes be recognized after careful observations of the rate of weight loss and of the basal metabolic rate during a period of dieting.

The beneficial effects of dietotherapy may be ascribed to the drop in metabolic rate which follows upon moderate restriction of diet. Excess fatty tissue alone is removed and accounts for the feeling of well being and increased resistance to fatigue observed in individuals so treated. It is well to remember that the dietary treatment of obesity is still the most important and satisfactory therapeutic method, and cannot be replaced by medicinal agents.

When obesity is complicated by pathologic conditions the principles of treatment remain virtually the same. Undernutrition is the method of choice in all instances except those associated with diseases of the biliary passages; here the procedure must be slow. In diabetes, as Allen has long ago pointed out, undernutrition is the ideal method of desugarization; and on account of the frequent association of obesity with diabetes, reduction of weight is accomplished at the same time by this means. In cardiac and circulatory diseases restricted food intake is of the utmost importance. Its beneficial effects are traceable to many influences; chief of which is unquestionably the reduction in the basal metabolism. The influence of this factor on the circulatory system has come to be appreciated only since the recent work of Blumgart referred to earlier in the discussion. It relieves the physiologic strain caused by the obesity on the metabolism. Combustion of body fat and removal of retained water add to the effectiveness of undernutrition. As the digestive functions in such cases are more often impaired than not, the administration of the Karrel diet is a simple and suitable way of accomplishing the desired result. It is in this group of cases, where prompt elimination of retained water is so desirable that the employment of diuretic agents such as salyrgan or neptal, calcium, etc. are particularly useful.

To summarize then, obesity is a condition which results from the exaggeration of a physiologic process and culminates in the accumulation of excess fat. The chief factor in this process is the inequality between food intake and energy output. In certain instances, disease of the central nervous system or dysfunction of the endocrine glands so affects the metabolism of the body as to favor and accelerate the generalized or localized deposition of fat. In close association therewith, water is retained in the tissues. The joint effect of the accumulation of fat and water may be detrimental to the efficiency of the circulatory apparatus, may affect the activity of the endocrine glands and impair the functions of the liver and pancreas, leading to other diseases. It may further undermine the vitality of the whole body so as to render it susceptible to a variety of accidents.

The rational treatment of obesity is based upon the reversal of the physiological process which leads to the deposition of fat. It aims to reestablish a balance between the output of energy and the intake of food. The aid derived from the use of medicinal agents is directed largely toward the acceleration of metabolism and the elimination of water; these measures appear necessary in a restricted number of cases and are at best, of limited effectiveness.

A CRITICAL ESTIMATE OF THE VALUE OF LABORATORY PROCEDURES IN DISORDERS OF METABOLISM*

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If I had chosen the title for this talk I should be guilty of presumptuous arrogance. As your entertainment committee wished it upon me, I can only feel flattered that they should have believed me capable of condensing such a subject into 45 or 50 minutes, especially after I had recently displayed my incapacity by expending on the same subject, with my friend Van Slyke, some 1200 pages of rather fine type. I pity you for the disappointment that is in store for you and may as well confess that I have substituted for the expected abstract, which is clearly beyond my powers, some general reflections on the place of the chemical analysis of blood in medicine which have only the weight of my personal opinions unless the practical illustrations which I shall offer may lend them some interest and conviction.

It is hard to believe that in this subject almost the whole of the great mass of literature and knowledge (the two are quite distinct) has been developed in the course of two decades, since Bang, Folin, Van Slyke, Benedict and others presented to the physician, at just the moment when venous puncture was becoming a common procedure, practical methods for the analysis of blood. These methods, born in the physiological and chemical laboratories were put into the hands of clinicians who had neither the analytical training to utilize them, nor the physiological and chemical education necessary for their interpretation. This is not said entirely in a spirit of criticism; because there is reason to be proud that clinicians have been found with critical judgment and industry great enough to overcome these initial handicaps. Their contributions have not

* Delivered October 31, 1933.

been confined to pathology, but have extended back to the mother sciences of physiology and chemistry. Nevertheless, this knowledge was secured by the noblest only after false steps. Furthermore, as in all virgin fields, no step of any kind could be taken without the discovery of something new and these discoveries came in such confusing profusion that it was impossible to take time to separate gold from dross. The great mass of exploiters, trained in a purely clinical field and reasoning in the usual simple and direct manner, that no two things can coexist without being related, immediately began to connect chemical abnormalities with specific diseases, without consideration of the fact that physiology deals with functional disturbances and cuts along other lines than pathology. Too many of these conclusions reached in the first heyday of excited exploration have received the unmerited sanction of tradition and threaten to be transmitted as part of accepted medical lore to the next generation, which deserves better at our hands.

It is, perhaps, deplorable that clinical chemistry sprang into active life during the period of therapeutic nihilism when medicine felt its duty done if it gave the patient a name to die by, perhaps illuminating it with a placebo. This spirit only exaggerated the tendency mentioned above, to connect diseases with chemical abnormalities and, for a long time, diverted attention from what is at least as important an aim of physiological chemistry, the logical direction and control of the treatment of the disorder which the analyst has revealed. The clinician, meantime, was provided with his chemical tools only one at a time—to be sure in such rapid succession that he had not time to perfect himself in the use of one before the next appeared. Nevertheless those which custom had made first familiar received a lasting preference which has given them undue authority, to the exclusion of others. The continuous appearance of new models of old techniques made selection even more difficult. As these new models were frequently simplifications and not improvements, preference was too often given to inferior procedures.

Technical complexities of procedure and the special knowledge required for proper interpretation has had its usual effect in segregating a province of medicine. There is no escaping the necessity of therapeutic specialization; it is, however, regrettable that this leads to restriction of vision by separation along artificial lines. The term "diseases of metabolism" implies a most unfortunate line of separation. I may say that the only change I was permitted in my title was the substitution for this opprobrious epithet of the term, "disorders of metabolism". From the therapeutic standpoint the treatment of diabetes, nephritis and certain endocrine disorders requires more experience and special knowledge than that in the possession of most practitioners. More important is the fact that to conduct such treatment in an efficient and economical manner necessitates a prohibitive expenditure of time and effort unless there is enough work to warrant the maintenance of a certain amount of special organization and machinery. Specialization on the basis of techniques is, however, dangerous, whether the technique be that of electrocardiography, roentgenology, or chemistry, if the specialist loses sight of the general problems of physiology and pathology or the general practitioner becomes unable to evaluate the special examinations. Nothing but evil can come of a situation in which the discovery of glycosuria by the practitioner is the signal for a diagnosis of diabetes and a note to a metabolism clinic; although this may be preferable to retention of the patient and unintelligent treatment. If, on his part, the expert has become so narrowed in his outlook that he allows the patient to die of tuberculosis in behalf of diabetes, his value to medicine is somewhat fictitious.

This is, however, a small issue compared with the fact that a few particular diseases which manifest themselves chiefly in disturbances of metabolism have come to be considered the peculiar province of the metabolic specialist and his techniques. This division has deprived the general clinic of the benefits of one great branch of physiological

knowledge, has restricted the machinery for the investigation of metabolic disorders and has robbed the specialist in his corner of the advantages that would come from wider comparison and analogy. This leads inevitably to the treatment of diseases rather than patients. There are no diseases of metabolism. There are no diseases that are not attended by disorders of metabolism, because metabolism is the sum of those processes by which life and its functions are maintained. There is no reason to believe that rectification of these disorders is superfluous because the disturbances do not dominate the picture, because they are not detectable by conventional routine procedures, or because their treatment does not strike at the fundamental cause of the disease. After all, diabetes itself can at this moment be looked upon only as a symptom complex and, insulin to the contrary notwithstanding, is treated only by palliative, symptomatic methods.

My plea, then, is not for less chemistry, whether it is measured in procedures or their application, but for more chemistry, and better chemistry, more widely and thoughtfully employed. I should like multiplication rather than restriction of procedures with careful selection in each case of those best adapted to give the most useful information, not the endless repetition in all patients of some especial "blood chemistry routine", too often chosen because it fits some system of blood analysis devised for the convenience of the analyst. Finally I would have the chemical data examined and interpreted, not as things apart, but with due recognition of all other available information. Nor should the scope of examination along any other relevant line be limited by the fact that a metabolic disorder dominates the clinical picture.

The common statement, that a chemical procedure is good enough for clinical purposes should arouse suspicion at once. First of all, it implies that selection has been determined by the convenience of the technician with the patient as a secondary consideration. Moreover, it suggests a carelessness of attitude that engenders feelings of un-

Table 1. The distribution of chemical substances between cells and serum and the effects of cell volume on whole blood analysis. The data are collected from various sources, many from data secured in the author's laboratory (See footnotes, following page).

Substance	Standard of Measurement	Plasma	Cells	Whole Blood	
				Normal[1]	Anemic[2]
Total protein	per cent (N × 6.25)	7.0	35.0	19.5	15.2
Hemoglobin	per cent	0	35.0	15.6	8.4
Serum albumin	per cent	5.0	0	2.8	3.9
Serum globulin	per cent	2.0	0	0.9	1.6
Total non-protein nitrogen	mg. per cent	29	49	39	33
Urea nitrogen	mg. per cent	19	17	18	18
Uric acid[3]	mg. per cent	3	3	3	3
Creatinine[4]	mg. per cent	1.2	1.2	1.2	1.2
Creatine	mg. per cent	0	6	2.7	1.4
Amino acid nitrogen	mg. per cent	6	10	7.8	6.9
Glucose[5]	mg. per cent	96	75	86	91
Sodium	mg. per cent	310	+[6]	172+	241+
Potassium	mg. per cent	18	420	197	107
Calcium	mg. per cent	10	0	5.6	7.8
Magnesium	mg. per cent	2	5	3.4	2.8
Bicarbonate	CO_2 content (vol. per cent)	68	45	58	63
Chloride	mg. per cent	362	192	285	323
Inorganic phosphate[7]	mg. per cent of P	3	3	3	3
Organic phosphate	mg. per cent of P	0.5	52	24	12
Fat	mg. per cent of fatty acids as tripalmitin	355	?[8]	?	?
Lipoid phosphates	mg. per cent of P	9	16	12	11
Cholesterol	mg. per cent	207	?[8]	?	?

certainty. Surely nothing is to be gained by straining at chemical gnats and swallowing clinical camels. But medicine has quite as much dignity as the other biological sciences and it behooves the clinician to treat it with due respect himself and to resent any slurs that may be cast upon it by snobbish chemical confreres. Not only must the clinician assure himself that a chosen technique is capable of the desired accuracy, but he must assure himself that it is being applied, with adequate controls, by persons who are proficient enough to secure this accuracy. His duty does not, however, cease at this point. It is a waste of time and effort to strain for analytical accuracy on unsuitable material. The aim of clinical chemistry is to gain information concerning disorders of life processes, not *post mortem* changes. In blood, shortly after it is drawn, glucose begins to decompose, with formation of lactic acid; the organic and inorganic phosphates may undergo certain permutations; nitrogenous compounds are broken down by the action of bacteria and enzymes. All of these changes are retarded by keeping blood cold, sterile and out of contact with air; some can be prevented by the use of preservatives of the proper kind. But these measures are only palliative; the only true corrective is to reduce to an absolute minimum the interval between collection and analysis of blood.

For certain analyses only serum or plasma can serve; blood is useless. This is especially true of inorganic analyses. The reasons will be obvious from Table 1. In

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[1]Oxygen capacity 20.9 vol. per cent (15.6 gm. per cent hemoglobin), cell volume 44.5 per cent.

[2]Oxygen capacity 10.45 per cent (7.8 gm. per cent hemoglobin), cell volume 22.25 per cent.

[3]Uric acid values and distribution are somewhat uncertain.

[4]The distribution of creatinine is not entirely certain.

[5]These figures are from Somogyi and represent true glucose. Cells contain larger amounts of reducing substances other than glucose. Therefore analyses by the usual methods indicate a somewhat different distribution.

[6]It has been assumed that the cells are free from sodium, but they may contain minute amounts of this element.

[7]By inorganic phosphate is meant total acid soluble phosphates — inorganic phosphates, i.e., phosphate esters.

[8]The distribution of fatty acids between cells and plasma is still uncertain.

this table the first two columns show the distribution of a variety of substances between cells and serum of average normal blood, the third column, the concentrations of the same substances in whole blood. The fourth column represents the effects on whole blood of reducing the cells 50 per cent (that is, producing an anemia) while the concentrations of all substances in serum and in cells remain the same. It is at once evident from the table that about those substances which are most unevenly distributed whole blood analyses can give no useful information. From examinations of whole blood it would seem that chloride, sodium and bicarbonate were increased and calcium, potassium and creatine diminished in all patients with anemia, although the concentrations of these substances in both cells and serum are entirely normal.

When blood is exposed to air it loses carbon dioxide and takes up oxygen. Simultaneously the cells contract somewhat, yielding water to the plasma. Therefore, if the chemical constitution of serum is to be determined, strict accuracy demands that the blood be taken, preserved and centrifuged without contact with air. This is of the greatest importance if knowledge of its CO_2 content is desired; however, neglect of these precautions may introduce an error of no negligible magnitude in the determination of cell volume, chloride, proteins and sodium. Certainly, if serum analyses are contemplated, more than the usual care must be taken to prevent decomposition of blood and to expedite analysis. Errors due to air exposure are small compared with those that result if any degree of hemolysis is produced by careless handling. Furthermore, anticoagulants can not be employed with impunity because they may also alter the volume of the blood cells. The use of serum, rather than plasma, for analyses has much to recommend it. Personally I believe that more useful information could be secured if, in spite of the additional trouble involved, serum was rather widely substituted for whole blood. Such an expedient as the new Folin method of securing so-called "unlaked blood" filtrates has too many elements of uncertainty and is, at

best, limited in its application. The point I wish to emphasize, however, is that the physician who sends blood for chemical examination must know, not only what analyses may be of advantage, but also enough about the technique of drawing and preserving blood to avoid prejudicing all the efforts of the chemist. A word may be added concerning the technique of venipuncture. In conditions of venous stasis fluid passes out of the blood stream into the tissues. If venous obstruction is maintained for 5 or 10 minutes as much as 10 per cent or even more of the water may escape from blood and this change is accompanied by disturbances in the concentration of most of the chemical constituents of the blood. Analyses of samples collected under these circumstances can give only a sorry impression of the actual composition of blood circulating in the vessels of the patient.

Of the substances listed in Table 1, which is far from complete, the average physician confines his interest to three or four constituents. Hemoglobin is, of course, relegated to the non-chemical technique of the clinical pathologist. Serum proteins and their fractions, albumin and globulin, are only beginning to become popular in the classification of nephritis, while their value for other purposes is little appreciated. Loss of protein into the urine is not the only condition which depletes serum albumin. This fraction of the proteins diminishes in all conditions of malnutrition (protein starvation) and, when for this reason it falls below a certain level, edema as surely appears as it does in nephritis when a comparable reduction of albumin results from proteinuria. Moreover, in malnutrition, as in nephritis, it is the albumin fraction which suffers. Diagnosis in cases of edema of obscure origin would be measurably advanced by more frequent serum albumin determinations and the physician would regard with less equanimity the discomforts of a patient on a diet containing insufficient protein if a report of low serum albumin gave him objective evidence that the subject was starving. During the treatment of diabetic acidosis it is quite unfashionable to omit determinations of blood sugar and carbon

dioxide. Yet there is much evidence that neither hyperglycemia nor acidosis is of such imminent importance as the dehydration and concentration of the blood that accompany this condition and finally lead to fatal shock. I do not wish to disparage the value of sugar and carbon dioxide determinations; but would add some measure of the water content of the blood. For this purpose, repeated estimations of hemoglobin may serve, but determination of serum proteins is superior. It is even more useful in estimating the effects of fluid administration in other more chronic dehydrating conditions. And may I add, without offense to the cardiologists, that under the most meticulous chemical guidance the clinician is not relieved of the necessity, even in diabetic acidosis, of observing with watchful care the state of the peripheral circulation, and especially the blood pressure, which gives the most reliable and earliest warning of the onset of shock.

Serum globulin reacts to quite other influences. It is little reduced by albuminuria and nutritional disturbances, unless these are caused or attended by infections. It is found elevated in most infectious diseases, especially if there are extensive ulcerations or suppurative processes. Tuberculous or syphilitic ulcerative conditions appear to have a particularly striking effect. In kala azar extremely high values are observed and are the basis for Ray's hemolytic diagnostic test for this disease. The disease in which it may reach the greatest heights, however, is multiple myeloma. The association of extreme globulinemia with anemia and rarefaction of the bones may establish the diagnosis of myelomatosis in a patient who fails to excrete Bence-Jones protein in the urine. Such a case in our own clinic had been given a diagnosis of hyperparathyroidism because of the presence of extremely high calcium and low phosphorus in the serum and a negative calcium balance. The discovery of 9 per cent of globulin in the serum, instead of the usual 1.5 to 2.5, established the diagnosis which was confirmed at autopsy, when the parathyroid glands were also found to be entirely normal. Obviously determinations of serum proteins and their fractions

should not become part of a routine chemical system indiscriminately applied, but may give information of great value for diagnosis and the direction of treatment, if they are employed with discernment.

About non-protein nitrogenous constituents, since the pioneer articles of Folin and the early work of Myers, has developed a tradition that leads to unnecessary work in the routine determination of nitrogen partitions. In general, urea makes up so large a fraction of the total non-protein nitrogen that it is almost a matter of indifference which of the two is chosen, unless determination of the urea clearance is intended. If serum proteins are to be measured at the same time the total non-protein nitrogen must be determined any way and urea is more or less superfluous. Only in the last hours of diseases with profound liver damage is any information of advantage secured by measuring both non-protein nitrogen and urea. In these conditions, when the liver is no longer capable of breaking up the amino acids and the kidneys are incapacitated, the blood urea may be found normal or low, while non-protein nitrogen is greatly elevated. In the present confused state of knowledge of uric acid and purine metabolism we are at a loss to explain abnormalities of blood uric acid. The reputation which this substance enjoyed in the diagnosis of renal disease is exploded. Even for the diagnosis of gout it has proved of little value because it is so frequently and inexplicably high in other conditions and may be normal in outspoken gout. On the other hand, this disease is so often accompanied by arteriosclerosis and kidney disease, that its victims deserve careful examination of renal function.

The concentration of creatinine is seldom increased unless there is grave kidney damage. For this reason, importance has been attached to it as a criterion of prognosis in nephritis. It is quite generally stated that if blood creatinine exceeds 5 mg. per cent early death may be expected. This is true only in chronic renal diseases. Higher values, found in severe acute nephritis or in surgi-

cal diseases of the kidney, are compatible with recovery. Because creatinine rises only in the terminal stages of chronic nephritis, when urea has reached high levels, its determination in mild or early nephritis or in forms of the disease which are not associated with nitrogen retention is superfluous. After all, prognosis is not the chief aim of medicine. Creatinine gives little indication of the efficacy of therapeutic measures. Attention should be called to the use of creatinine excretion as a measure of renal insufficiency. It is becoming increasingly popular, although it is still uncertain whether it has any advantages over some of the simpler tested methods. On the whole determination of creatinine is among the measures that should be employed only in selected cases, when blood non-protein nitrogen and urea are elevated.

The impression is altogether too wide-spread that high blood non-protein nitrogen or blood urea is pathognomonic of kidney disease. So far is this idea carried that the degree of nitrogen retention is frequently used as a measure of the severity of renal injury. No basis for such a concept can be found in physiology. The non-protein nitrogen content of the blood may be considered as the resultant of three factors: the rate of destruction of protein in the body, the concentrating powers of the kidneys and the amount of water excreted. If the destruction of nitrogen is great enough, as it may be in such profound intoxications as lobar pneumonia, the blood non-protein nitrogen may rise even when the kidneys are sound, especially if water excretion is small because the patient has received too little fluid. Such increases, even when they have attained considerable magnitude, may disappear overnight if the urine volume is augmented by the administration of more fluids. Persistent vomiting—for example, in pyloric stenosis—may so deplete body fluids that the urine becomes extremely scanty merely from lack of available water. High blood non-protein nitrogen results, and responds again to parenteral administration of fluids. In these circumstances nitrogen retention should be considered not as an indication of renal disease, but as evi-

dence of toxemia and dehydration and may serve as a warning. If, for any reason, in nephritis, the urine volume is reduced, or protein destruction exaggerated, a kidney which could, under favorable circumstances, perform its function in a satisfactory manner, may be unable to excrete enough nitrogen. Gastro-intestinal disturbances, febrile diseases, and heart failure are the conditions which most frequently bring about such states of renal decompensation. With the relief or disappearance of these complications the blood non-protein nitrogen may return to its normal level. On one occasion in my experience a stuporous state, anuria and a non-protein nitrogen of 321 mg. per cent led to an initial diagnosis of uremia, diverted therapeutic efforts, and delayed operation in a patient with pyloric obstruction who proved, at autopsy, to have normal kidneys. An old woman with generalized arteriosclerosis involving the kidneys, and congestive heart failure, had a blood non-protein nitrogen of 140 mg. per cent. With rest and digitalis this fell rapidly to normal limits and, just before she died from carcinoma of the rectum, 18 months later, was only 40 mg. per cent. These are only two of many examples that could be given of the fallacy of interpreting non-protein nitrogen in terms of renal pathology only, the dangers of drawing conclusions from single determinations, and the information concerning the efficacy of treatment that may be gained by frequent examination of the blood. It must be recognized that no one of the nitrogenous compounds of the blood rises in uncomplicated renal disease until kidney destruction is far advanced.

The difficulty involved in the preparation of blood serum as well as the actual chemical procedures employed, has restricted the determination of the inorganic constituents of blood largely to research laboratories. And yet no chemical properties of the body are more solicitously guarded or more important for the proper conduct of the vital functions than the concentration and pattern of salts in the body fluids. On these depend, among other things, the

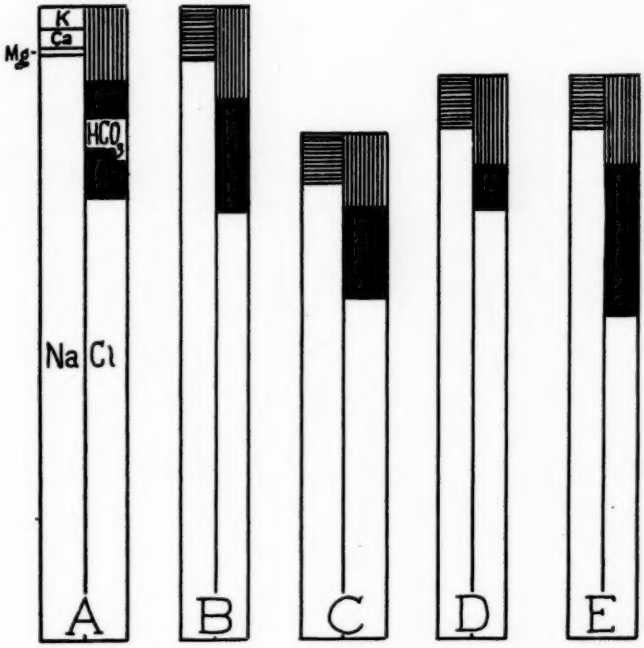

Fig. 1. Schematic representation of electrolyte patterns of the serum in conditions associated with dehydration. The concentration of electrolytes is indicated by the height of the columns, the volume of the body fluids by their width. The unlabelled, vertically ruled segments represent the proteins, phosphates, sulfates and organic acids. Except in A the bases, K, Ca and Mg, have been treated as a single unit, horizontally ruled.

A. Normal average. B. Proportional reduction of water and salt. C. The result of restoring the water, but not the salt in condition B. D. and E. Loss of 1/5 of the volume of the body fluids and an extra 1/10 of the salts. In D the salt has been lost chiefly in the form of bicarbonate, in E, chiefly as chloride. The latter is the picture of pyloric obstruction or profuse vomiting of hydrochloric acid; D may be encountered in severe diarrheas.

maintenance of both osmotic and acid-base equilibria. Everyone in the audience is familiar with the fact that blood cells and other cells, when their normal environmental medium is diluted with water, swell and finally rupture. If they are diluted with an isotonic salt solution they neither swell nor rupture. In life dilution of the body fluids has deleterious effects which can probably be ascribed to phenomena of the same nature, although they do not usually proceed to the point of cell destruction. Administration of excessive water to animals produces symptoms of intoxication which may be fatal. That these are referable, not to expansion of the body fluids, but to dilution of salts in those fluids, can be inferred because administration of equal amounts of normal salt solution produces no symptoms and because, when symptoms have been provoked by water administration, they can be relieved by giving salt. If the salt supplies have been previously depleted less water is required to induce intoxication. This is illustrated by miner's or stoker's cramps. Miners and stokers who lose enormous amounts of salt by sweating during the performance of heavy labor at high temperatures, are prone to develop cramps when they slake their thirst with water. These symptoms can be prevented or relieved by the administration of salt. Undoubtedly water intoxication is not uncommonly provoked by physicians who, with the best intentions, employ water without salt to combat dehydration.

In Fig. 1, the two columns at the left illustrate schematically the composition of the salts found in the serum. In order that comparisons may be facilitated concentrations are given not in the conventional terms of mg. per cent, but in terms of combining equivalents (milliequivalents per liter, m.eq.), a usage which is becoming more and more general. (Let me remind those who find the term m.eq. strange, that it has the same significance as c.c. of 10th normal solution per 100 c.c., the conventional standard for the measurement of acidity of gastric contents and urine.)

In a medium so nearly neutral as blood serum the bases cannot differ appreciably from the acids. For this reason determination of the bases affords a measure of the total salt concentration in serum. Because sodium makes up such a large fraction of the total base, analysis for this element yields practically the same information. Conditions which cause dehydration invariably deplete the salts of body fluids, chiefly at the expense of sodium. Whether this salt depletion is demonstrable by blood analysis depends on the proportions of salt and water which are lost. Analyses of blood, unfortunately, give no information concerning the absolute quantity of any substance in the body, but only of its concentration. In the figure the difference is indicated by the two dimensions of the columns. Concentrations are represented by the height, the volume of the body fluids by the width of the various columns. For example, Figure 1 B, in which the columns are narrower by 1/5th, but the same height as those in A, illustrates a condition in which 20 per cent of the water of serum has been lost with an equivalent amount of salt. In spite of these great losses, beyond a slight increase of the proteins the chemical pattern of the serum is practically normal. C represents the result of restoring the water of the body, without salt. This is the condition in water intoxication. The actual deficiency of body salts in B and C is the same, but it is demonstrable by chemical analysis only in C. Usually in conditions of dehydration salts are lost somewhat in excess of water, yielding pictures like D and E. In both the fluid volume has been reduced 20 per cent, salt an additional 10 per cent. Confronted by such a situation, it is obviously necessary to give salt and water in amounts and proportions so adjusted that both the volume and the composition of the body fluids will be restored to normal. The quantities of salt and water required can not be estimated by any exact rule. In general, in addition to normal saline some extra water or glucose solution is usually needed to offset the continual slight dissipation of water without salt by the lungs and skin. Every effort must,

however, be made to restore body fluids without producing the water intoxication picture illustrated in C.

The ideal criteria for the evaluation of the degree of dehydration would be analysis of the serum for base or sodium and measurement of the body fluids. The latter is impossible. Imperfect information can be secured by serum protein or hemoglobin estimations; but these, at the best, only measure hemoconcentration, which is influenced not only by the volume of fluid in the body, but also by its distribution. Furthermore, hemoglobin and protein may have been affected by pre-existing anemia, or malnutrition. At present we must depend for the estimation of the state of the fluid supplies of the body upon clinical observation of the state of the mucous membranes, the elasticity of the skin, intraocular tension, the state of the circulation, etc. During treatment measurements of the base or sodium of serum would aid greatly in the regulation of fluids. Unfortunately, the procedures now available for the determination of total base or sodium require so much time that their practical utility is very small in the conditions of emergency for which they are most needed. If attention is turned for the moment to the acid columns of the figure it will be apparent that bicarbonate and chloride make up the great bulk of acid, with chloride predominating. Together they almost balance the sodium. It follows, as figures C, D and E indicate, that any important change of sodium will be reflected in the sum of bicarbonate plus chloride. Therefore, this sum may be used as a practical measure of the total base or sodium concentration of the serum.

Considering the relative simplicity of the procedures for the measurement of carbon dioxide and chloride and the frequency and seriousness of dehydration, it is both surprising and distressing that this combination of tests is not more generally employed in the clinic. It would be fair to say that there are few conditions in which the most satisfactory information can be secured by either test alone. Even in diabetic acidosis sodium and chloride are

depleted quite as much as bicarbonate—or more—and their restoration is quite as important. It may be well, for a moment, to consider a few of the common conditions attended by dehydration and salt depletion of clinical magnitude. One of these, diabetic acidosis has been twice mentioned already. In this condition, if shock is prevented and body fluid and salt restored, all the alarming symptoms may disappear while the blood sugar is still greatly elevated and serum bicarbonate reduced and while glycosuria and acetonuria persist.

Vomiting sacrifices both salts and water. Its effect on serum and other body fluids depends on the duration and severity of the vomiting and the nature of the vomitus. If the latter is highly acid a condition like that depicted in E results; chloride becomes especially depleted, while bicarbonate may be normal or high. Sodium and water always suffer and, if the vomiting has been sufficiently severe and prolonged, the loss of sodium usually exceeds that of water. This becomes evident in the serum in reduction of the sum of bicarbonate and chloride. Determination of these two substances may aid in establishing a rapid diagnosis of the nature and severity of the vomiting. In functional gastro-intestinal disturbances or psychoneurotic vomiting the chemical pattern of the serum is less often disturbed because, despite appearances, patients with these conditions usually retain enough food and fluids to escape serious dehydration and salt depletion. However, as usual, chemical examination of the blood is more important as a guide to therapy than as an aid to diagnosis. In organic obstruction of the intestinal tract operative interference is far better tolerated if dehydration is first overcome and the salt content of the body fluids restored. Subcutaneous or intravenous administration of large amounts of sodium chloride and glucose solutions should precede operation. In the treatment of peritonitis or paralytic ileus the same treatment is indicated. The efficacy of these measures can well be checked at frequent intervals by chemical examination of the serum to

learn whether the proportions of salt and water have been well chosen.

The dehydrating and salt-impoverishing effects of diarrhea have been recognized since Carl Schmidt published his famous monograph on epidemic cholera in the middle of the last century. They have, however, received too little therapeutic recognition outside of the field of pediatrics.

Loeb has recently pointed out that the most striking and consistent disturbance of metabolism in Addison's disease is reduction of the sodium concentration of the serum. In the absence of the suprarenal glands the kidneys apparently allow sodium salts to escape in excessive amounts into the urine. During the acute crises of the disease the sodium of the serum is low and symptoms may be alleviated by the administration of large amounts of salt. During the more chronic stages the concentration of sodium in the serum may be normal; but if salt is withdrawn from the diet, rapidly falls to a subnormal level. This effect of salt restriction on serum sodium (or bicarbonate and chloride) may prove an aid in the diagnosis of Addison's disease; but must be checked by frequent analyses of serum, because, if the restriction is prolonged too far a serious crisis may be precipitated.

In lobar pneumonia and other acute febrile diseases, if insufficient fluids and salt are given, sodium and chloride are also wasted and their concentrations in serum fall. Here again the regulatory powers of the kidney appear to be lost and care should be taken to provide enough salt in the diet to replace the wastage.

If the circulatory and renal systems are competent, and sufficient absolute amounts of salt and fluid are given to satisfy the requirements of the organism, the kidneys will make the necessary finer adjustments by excreting any excess of water or salt or even individual ions. For example, in the vomiting of pyloric obstruction there is sacrificed more chloride than sodium. Apparently the most efficacious treatment, if it were feasible, would be the

administration of hydrochloric acid in addition to sodium chloride. However, if enough fluid and sodium chloride are given to induce a free flow of urine the kidneys will excrete more sodium than chloride, thus restoring the normal electrolyte pattern of the serum. If, on the other hand, insufficient amounts of salt and fluid are given or the kidneys are not competent, such secondary adjustment is impossible and both the quantities of fluid and salt given and the nature of the salts must be regulated with the greatest care. Under these circumstances, especially, the concentrations of bicarbonate and chloride in the serum must be watched with the greatest care and frequency if the patient is to receive therapeutic justice. The simple excretory function of the kidney has been too much stressed, the selective discrimination with which it is exercised has received little thought. Uremia is generally looked upon as an intoxication resulting from the retention of excretory products, although an equally good brief could probably be prepared for the theory that it is due to wastage of materials through incompetent kidneys.

The only definite and consistent result of reduction of renal substance is the passage of dilute urine, usually in uncommonly large amounts, loss of concentrating power on the part of the kidneys. Apparently the urine becomes more like a simple filtrate of serum. Those solutes, like the nitrogenous constituents, which are usually excreted in high concentration are less efficiently eliminated, while solutes, like sodium and chloride, which usually appear in lower concentration in urine than in blood, are now more highly concentrated and, therefore, wasted. The acidosis of nephritis is due less to accumulation of foreign acids in the blood than it is to excessive loss of the base, sodium. Dehydration and salt depletion are regularly found in terminal stages of renal disease, although the former is often masked by the presence of edema due to heart failure. The inability to prevent salt wastage is well illustrated by the course of the case depicted in Figure 2. The patient, a male, 42 years old, was admitted with hyper-

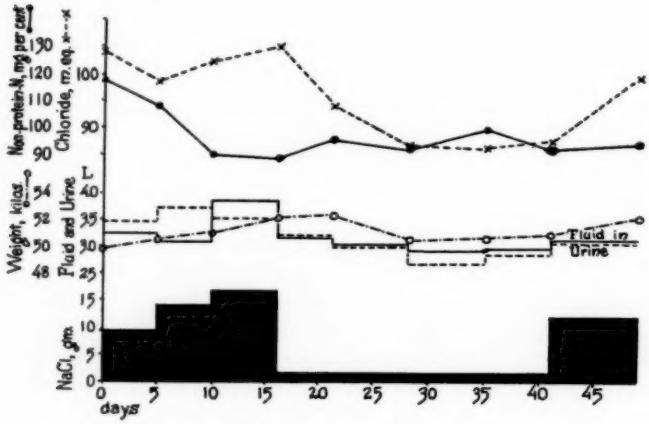

Fig. 2. The effect of varying salt in the diet of a patient with renal insufficiency. In the top section are represented the course of the non-protein nitrogen of the blood and the chloride of the serum; in the middle section, the obvious fluid ingested, the urine volume and the body weight; in the bottom section, the sodium chloride of the diet. On the 25th day the concentration of total base in the serum was only 126 m.eq.

tension, hypertrophy of the heart, irregularities, murmurs and electrocardiographic signs that suggested rheumatic or coronary heart disease, a urine of low specific gravity, with moderate amounts of albumin, red and white blood cells and casts, a phenolsulfonphthalein excretion of 16 per cent in 2 hours and a blood non-protein nitrogen of 96 mg. per cent, rising to 131 mg. after diuresis. The edema largely disappeared under the influence of rest and digitalis, but the blood non-protein nitrogen was little affected, although the urine volume was nearly 3000 c.c. per day. In the figure the black columns at the bottom indicate the quantities of chloride (as sodium chloride) which he received, the lines in the upper section represent the concentrations of non-protein nitrogen and chloride in the serum. In the middle are shown the weight, the intake of obvious fluid and the urine volume. The reduction of serum chloride under the influence of salt restriction is quite as great as one would expect in pyloric obstruction.

But, whereas in the latter condition far before chloride had fallen to this level in the serum, it would have disappeared from the urine, in the nephritic it continues to be excreted. It is also worthy of note that on 15 gm. of

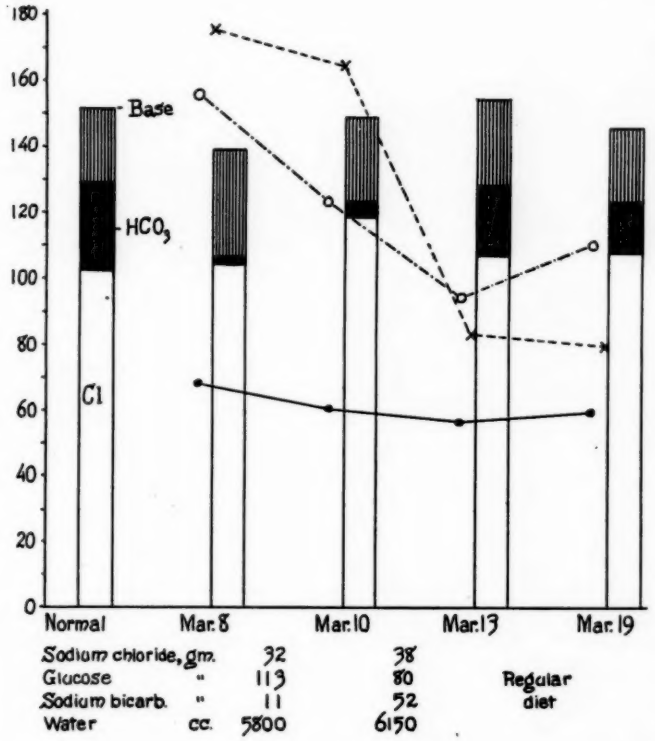

Fig. 3. The concentration of electrolytes in the serum of a patient with nephritis who had become dehydrated by vomiting. The concentration of total base is indicated by the total height of each column, the vertically hatched areas represent protein, phosphate, sulfate, and organic acid. The normal electrolyte pattern is shown, for comparison, on the left. All electrolyte values are given in m.eq. x — — — x = non-protein nitrogen of blood in mg. per cent. ·————· = serum proteins in gm. per liter. o—·—o = hemoglobin in terms of volumes per liter of oxygen capacity. The treatment is indicated below.

sodium chloride a day, although there was some retention of chloride and water, edema did not appear and the blood non-protein nitrogen fell. Determination of total base, when chloride had fallen to the lowest point, showed that sodium was wasted with chloride.

Although, in this case, it is impossible to connect the fall of non-protein nitrogen with the high salt regime, there is some evidence to suggest that salt depletion may be connected with nitrogen retention. This has caused certain members of the French school to speak of nitrogen retention from lack of salt. This implies a relation of cause and effect that is hardly warranted by the facts. However, attention may well be called to the fact demonstrated by Loeb and verified by Harrop, that blood non-protein nitrogen rises as serum sodium falls during the development of the acute crises of Addison's disease, while there is profuse diuresis.

A more striking instance of dehydration and salt depletion and the difficulties of adjusting the chemical pattern of the serum was presented in a review of salt and water metabolism some years ago. The patient, a man of 58, who for 26 years, following a fracture of the spine had suffered from incontinence of urine, was seen in consultation after spontaneous rupture of a perineal abscess had resulted in a urethral fistula which had been drained by operation about 12 days earlier. At this time he appeared greatly dehydrated, comatose, and his respirations were exaggerated. The serum electrolytes, the therapy which was practised and its results are shown in Figure 3. Again normal concentrations are indicated in the columns at the left of the figure. At the onset base, chloride and bicarbonate were all extremely reduced. After 2 days, during which he received large amounts of fluid, glucose, and sodium chloride, and some sodium bicarbonate, intravenously and subcutaneously, base had risen almost to, and chloride above the normal level, but bicarbonate was still extremely low. Dehydration had been partly overcome; both serum proteins and hemoglobin indicated that the

blood was less concentrated; and the blood non-protein nitrogen had begun to fall. The condition of the patient, meanwhile, had improved greatly. During the next three days administration of sodium chloride, glucose and water was continued vigorously, and in addition larger amounts of bicarbonate were given. At the end of this period the non-protein nitrogen had fallen almost 100 mg. per cent, the serum electrolyte picture was practically normal, respirations were quiet, consciousness was restored, and the patient was able to sit up and take food and fluids by mouth with relish. The points to which I wish to draw chief attention are: first, the simultaneous depletion of base, bicarbonate and chloride; second, the improvement that followed partial restoration of body fluids, and base, even when chloride was driven above and bicarbonate remained far below the normal concentrations; third, the necessity for administration of bicarbonate to meet the specific deficiency of this element in a subject who, because of impaired renal function, was unable, by exercising the usual selective activities of the kidneys, to make proper adjustments between ions.

Examples of this kind, involving a great variety of conditions not usually classified as diseases or disorders of metabolism, could be multiplied indefinitely to emphasize the value of chloride and bicarbonate determinations in the analysis, and in the treatment of patients with dehydration. However, these must suffice because I should like to touch on one other subject before closing.

With increasing knowledge of the chemical processes of bone formation and the effects of hormones and vitamins, analysis of blood has come to serve a useful purpose in the diagnosis of diseases of bone and disorders of calcification. There are one or two points to which I should like to call attention in this connection. First of all, the calcium of serum is not an independent variable. A certain fraction, which is apparently inactive, is combined with the serum proteins. Within certain limits, therefore, the concentration of calcium in serum varies with that of

protein. These variations seem to have no influence upon either calcification or muscular irritability. In order to interpret serum calcium in relation to these functions, protein should be determined at the same time. Secondly, bone is not composed of calcium alone, but also of phosphate and carbonate, particularly phosphate, and there is a tendency for calcium and inorganic phosphate of serum to vary inversely. For this reason phosphate should also be measured with calcium. Many erroneous impressions may be avoided if it is made part of routine procedure always to determine protein and inorganic phosphate of serum with calcium.

In every respect, but especially in relation to calcium and phosphate, the blood must be considered merely as a transportation medium. It serves to carry calcium and phosphorus from the gut, whence they are absorbed, to their great storehouse in the bones, or from the bones to the gut or kidneys by which they are excreted. From the concentrations of these elements in the blood serum alone, one can gain but an imperfect impression of calcium metabolism. Calcium in serum may rise either because it is being absorbed from the gut with unusual rapidity or because the bones are giving up excessive amounts. Low serum calcium may be referable to diminished absorption from the gut, increased deposition in the bones or accelerated excretion in the urine. The levels of phosphate and protein as determinants of serum calcium have already been mentioned. These and other factors that influence calcium solubility may be regarded as affecting the capacity of the transportation system. The causes of any disturbance of serum calcium and phosphate levels must be analyzed with consideration of all these variants, before a diagnosis can be made and therapy intelligently directed.

In Table 2 have been listed some of the most frequent causes of such abnormalities and the disturbances of function by which they are produced. It is quite evident that diagnosis from chemical examination of the serum alone must be highly unsatisfactory. It can be greatly

Table 2. The effects of various common physiological disturbances or diseases on calcium and phosphorus metabolism. O = no effect, — = diminished, + = increased. No distinction has been drawn between calcium and phosphate in relation to absorption, excretion and bone formation.

Condition	Absorption	Excretion	Bone Formation	Serum Ca	Serum P	Serum Protein
Vitamin D deficiencies	—	0	—	.	.	.
Rickets (in infants)—Osteomalacia (in adults) Usual picture in active stages				0 —	—	0
During repair or when diet is low in calcium or high in phosphorus				—	0 +	0
Fatty diarrhea. Probably improper absorption of vitamin Renal rickets. In some cases faulty absorption of calcium, benefited by vitamin D				—	0 +	0 —
Vitamin D excess. Associated with metastatic calcification	+	0 +	—	+	0 —	0
Parathyroid excess	0	+	—	+	0 —	0
Parathyroid deficiency	0	—	+	—	0 +	0
Thyroid excess	0	+	—	0	0	0
Thyroid deficiency	0	—	+	0	0	0
Acidosis or acidifying measures	+	—	—	+ —	+ 0	0
Renal rickets (osteoporosis) due to nephritic acidosis				—	+ 0	0 —
Conditions with low serum proteins Nephrotic syndrome	0 —	0 —	0 —	—	0 +	—
Malnutrition (protein starvation)	?	?	?	—	0	—
Osteitis deformans (Paget's disease). The serum picture and metabolic abnormality depend on stage and severity of the disease	0	+ —	+ —	+ —	+ —	0
Bone tumors—Serum picture depends on rapidity of bone destruction	0	+	—	0 +	0 +	0
Myelomatosis	0	+	—	0 +	0	0 +

facilitated by measurements of calcium and phosphorus intakes and outputs, but these require time and facilities that are rarely available. In most instances, however, a diagnosis can be established with the aid of x-rays of the skeleton and other types of clinical examination. This can, perhaps, be illustrated by description of a few cases.

A woman, 22 years old, was first seen in 1924, when she entered the hospital complaining of pains in her knees and hips and frequency of urination. Examination revealed fractures of the neck of both femora, patchy rarefaction of all bones, involving especially the pelvis, a urine loaded with pus from which streptococcus viridans was repeatedly secured in pure culture, a phenolsulfonphthalein excretion varying from 20 to 35 per cent and blood non-protein nitrogen slightly elevated. A diagnosis of osteomalacia was made. Although this long word has a satisfying sound, it is nothing more than a descriptive term. The important matter was to determine the cause of the softening and resorption of bone. The patient, who was followed for some years, entered the hospital repeatedly, usually because of fractures or some other symptoms arising from the disorder of calcification. During these years renal function continued to deteriorate under the influence of the infection, but she had few symptoms referable to the kidneys. The decalcification became gradually greater and more generalized. The results of chemical examinations of the serum are shown in Figure 4. The solid line, representing non-protein nitrogen gives a rough indication of the steady deterioration of renal function. Serum calcium is always reduced to a variable degree; phosphate lies at the upper limits of normal at first, rising somewhat as the disease progresses. Throughout the period of observation serum chloride was extremely high, while bicarbonate was proportionally reduced. A hyperchloremia (or chloride acidosis) of this kind is the typical effect of the administration of acidifying chloride salts such as ammonium chloride. As the administration of such salts leads to decalcification of the bones, it seems reasonable

to refer the osteomalacia in this patient, not to the usual deficiency of vitamin D, but to this endogenous chloride acidosis, which was probably connected with her renal insufficiency. Determinations of calcium and phosphorus alone, in this case, could have contributed but little, even if they had not proved positively misleading. There is evidence to indicate that acidosis is the immediate cause of many cases of so-called "renal rickets."

July 18, 1930 a white male, 60 years old, was sent to the hospital with a diagnosis of hyperparathyroidism. For three

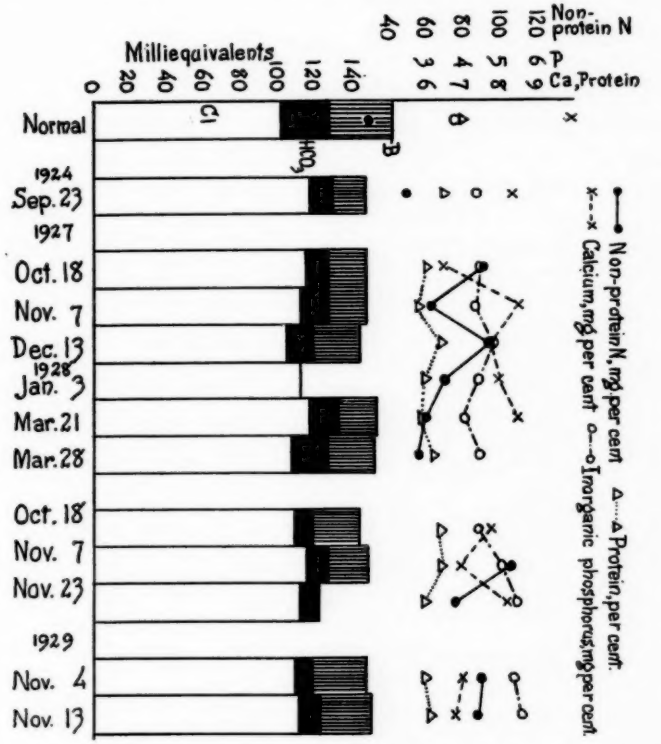

Fig. 4. Chemical changes in the serum of a patient with chronic renal disease and generalized osteoporosis.

years he had suffered from weakness, indigestion, anorexia and loss of weight, and increasing pains in his trunk and limbs. Extreme decalcification of the bones with some deformities, and a profound anemia with a high color index were discovered in November, 1929. The latter did not respond to oral treatment with liver and iron. Because of the weakness, general decalcification of the bones and high calcium in the serum, a diagnosis of hyperparathyroidism had been made. On admission he was desperately weak and emaciated. There was general decalcification of the bones with collapse of some vertebrae, and striking anemia with a high color index. He remained in the hospital until his death on Feb. 3, 1931. Both anemia and bone disorder defied all treatment and before his death he sustained many pathologic fractures. The calcium of the serum was very high, 12 to 18 mg. per cent, the inorganic phosphorus variable, 1.8 to 5.5 mg. per cent. With this picture in the serum and demonstrated negative balances of calcium and phosphorus, a diagnosis of hyperparathyroidism was warranted, according to the criteria proposed by Barr, especially since no Bence-Jones protein could be demonstrated in the urine. His serum proteins, however, proved to be extremely high, 9.8 to 13.0 per cent, in spite of a low albumin, 2.2 to 3.2 per cent. The serum protein was predominantly composed of globulin, which varied from 7.1 to 10.6 per cent. Because of this hyperglobulinemia and the anemia a diagnosis of general myelomatosis was made. At autopsy this diagnosis was confirmed and the absence of any parathyroid tumor or hyperplasia was also established. It has been claimed that decalcification of the bones with high serum calcium and normal or low inorganic phosphate is pathognomonic evidence of hyperparathyroidism. This is only one of many cases that prove the fallacy of this claim. Hypercalcemia has been reported by others and seen by us in patients with metastases of carcinoma in the bones. It is not unlikely that it indicates nothing more than the presence of a process causing exceedingly rapid destruction of bone. It can, therefore, be interpreted only with due consideration of x-ray findings

in the bones and all other significant clinical data which can be secured by other methods.

It may be relevant, in this connection, to mention that we have recently seen a case of hyperparathyroidism with no disturbance of calcium, phosphorus or protein in the serum. The diagnosis was established by the presence of diffuse decalcification of the bones with some tumors of the osteitis fibrosa cystica type and bilateral renal calculi.

The significance of abnormal concentrations of lipoids in the serum is still so obscure that the discovery of such abnormalities is of more interest than clinical value. Association of high serum fat and cholesterol with the nephrotic syndrome and certain types or phases of diabetes has long been recognized; but cannot be interpreted in terms that are useful for diagnostic or therapeutic purposes. There is good reason to believe, however, that as knowledge of lipoid metabolism advances, determination of serum fats, phospholipids and cholesterol will have to be added to the diagnostic armamentarium.

Part of the confusion of this chapter of blood chemistry may be due to general failure to recognize that lipoids, like proteins, are unable to traverse capillary membranes. For this reason, as Dr. Evelyn Man has recently demonstrated in our department, changes of blood water are reflected in proportional alterations in the concentrations of blood lipoids.

It may seem extraordinary that blood sugar has received no consideration. This omission implies no lack of appreciation of the importance of blood sugar measurements; it is prompted only by the fact that the subject has received so much more attention than other chapters of blood chemistry, that it has seemed best to devote the limited time at my disposal to the aspects of blood chemistry which have been less generally emphasized.

In conclusion I can only reiterate the opinions I expressed earlier: that it is unfortunate in the extreme to limit the application of chemical analysis of the blood to any selected group of technical procedures or to any one class of diseases, or to treat the information secured by these analyses as if it were separable or distinct from other types of clinical information.

CLINICAL OBSERVATIONS AND LABORATORY INVESTIGATIONS ON THE 1933 EPIDEMIC OF ENCEPHALITIS IN ST. LOUIS*

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St. Louis

Encephalitis, as it appeared in the epidemic in St. Louis in the summer of 1933, was an acute febrile disease, characterized by prominent signs of meningeal irritation, a comparatively short course, and a relatively low incidence of sequelae.

Early in the epidemic, hospitalization was strongly recommended by the Health Division, with the result that over 90 per cent of the reported cases were observed in hospitals. In the Isolation Hospital, where nearly 400 cases were treated, a senior student, responsible for the completeness of the records, was placed by Dr. Barr. The present report covers 300 of these cases, and free use has been made of the tabulations prepared by Mr. Robert L. Drury, a member of the senior class at Washington University.

Classification. The cases have been divided into three groups by Dr. T. C. Hempelmann[1]. The first two groups differ in the mode of onset, and the third group consists of abortive or very mild attacks in which the diagnosis was difficult and frequently uncertain.

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Read before the Annual Meeting of the Academy, January 4, 1934.

Onset and Initial Symptoms. The first type of onset was abrupt, and preceded by no prodromal symptoms. Headache and fever appeared, frequently associated with vomiting. Very rapidly the patients became somnolent, spoke slowly and with some difficulty, and at times went to sleep without finishing a sentence. A stupor from which the patient could be aroused to answer simple questions frequently followed closely on the appearance of somnolence, and in some cases true coma occurred. Mental confusion was commonly present. Instead of somnolence and stupor, many patients showed irritative phenomena, such as restlessness, constant irrational talking, or, rarely, active delirium.

The second type of onset was characterized by a prodromal period, usually lasting one to four days, in which slight fever and "grippy" feelings were usually present. At the termination of this period a sharp rise in temperature occurred, and the subsequent picture was similar to the first type.

The predominant features of the disease were meningeal

TABLE I.

TYPES OF ONSET

*Sudden	57.0%
Gradual	42.3%
Doubtful	0.6%

or meningo-encephalitic. Some degree of rigidity of the neck muscles was present in 86 per cent of the cases, and a positive Kernig's sign in 72 per cent. The abdominal reflexes were ordinarily absent, and the deep reflexes were diminished or absent. Plantar reflexes were abnormal in 40 per cent of the cases, but this was variable, and the findings would sometimes change from hour to hour. Tremors of the tongue and lips were frequent, and were especially noticeable when the patient attempted to speak.

* Any onset of less than three days duration was arbitrarily classified as sudden for purposes of tabulation.

Symptoms or signs referable to the eyes were comparatively rare, and usually consisted of small and sluggish pupils, blurred vision, or photophobia. Nystagmus and diplopia each occurred in 8 per cent, and strabismus and ptosis in 3 per cent and 2.6 per cent respectively. The accuracy of these last two figures is still open to some

TABLE II.

NEUROLOGICAL SIGNS

Abnormal deep reflexes	74.0%
Absent abdominal reflexes	59.6%
Tremors	55.6%
Abnormal plantar reflexes	40.6%
Aphasia or speech difficulty	12.0%
Facial weakness	6.0%

question, since it has not been possible to determine the condition of all of these patients prior to their attack of encephalitis, and since ptosis was more a weakness and slight drooping of the lids than an actual paralysis.

Mild and Abortive Cases. In some cases a slight fever of one or two days duration, with perhaps some stiffness of the neck or headache, prompted lumbar puncture, which revealed the increase in cells characteristic of encephalitis. At times an unexplained fever was the only symptom. In children the findings were more variable and mild cases seemed to be more common.

Spinal fluid. Lumbar puncture usually yielded a clear fluid under moderately increased pressure. In the majority of instances from 100 to 300 cells were present per c. mm., but this was subject to considerable variation, and one count as high as 1100 cells per c. mm. was recorded. Lymphocytes predominated, but in a few instances polynuclear cells constituted from 30 per cent to 50 per cent of the total count. At times the fluid withdrawn on the first puncture was normal, while a second puncture a day or two later showed the characteristic increase in cells. When the results of spinal punctures are tabulated, it is seen that 81 per cent showed 10 or more cells per c. mm. If, how-

ever, as is probably more correct, counts of 3 or more cells per c. mm. are considered abnormal[2], only 7 per cent of the cases showed normal cell counts.

A slight increase in globulin was demonstrated in 41 per cent by means of the Pandy test.

Sugar determinations usually showed from 50 to 90 mg. per cent, and very rarely was the result low enough to lead to a suspicion of tuberculous meningitis. Spinal fluid was precipitated as soon as collected, and the filtrate was used in determining sugar by the Shaffer-Hartmann method.

Blood. Blood counts most frequently showed white cells ranging from 10,000 to 14,000, with extremes of 2,800 and 36,000. With the Schilling differential, the usual result was a shift to the left.

Clinical Course. The clinical course was rather characteristic. Fever continued high, quite commonly between 104 and 105° F., for a few days, and then gradually diminished, in the majority of instances reaching normal in six to ten days after admission to the hospital. Frequently there was a critical drop in temperature, which then usually remained normal in uncomplicated cases. A few times the elevation of temperature was more prolonged, and in fatal cases the temperature usually remained elevated up to the time of death. Somnolence and stupor, when present, usually persisted until about the time of defervescence, and then rapidly disappeared, as did the other symptoms and physical signs. The rapidity of recovery in many instances was amazing, and at times a patient who at one visit could only be aroused with difficulty, would on the next day be alert and apparently perfectly normal.

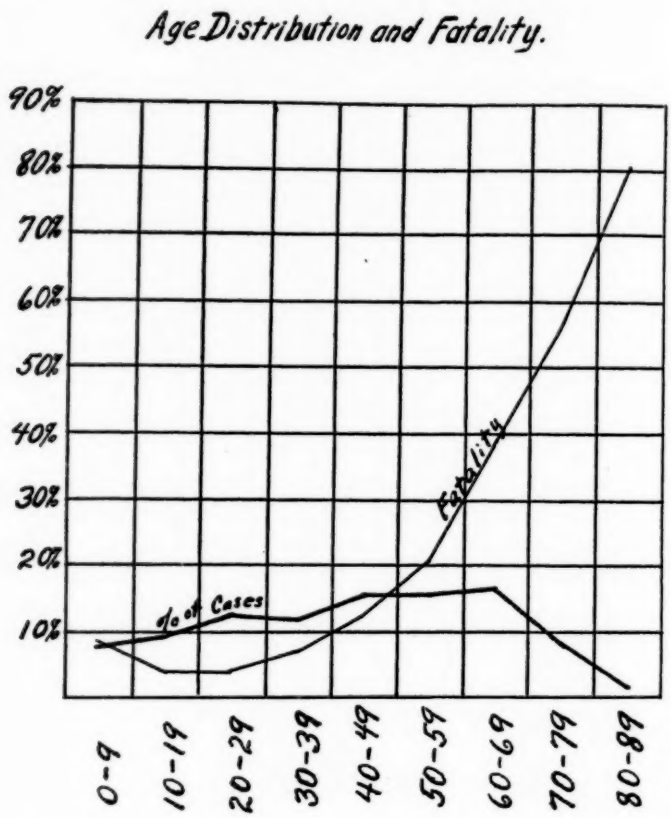
TABLE III.

*DEFERVESCENCE (200 CASES)

By lysis	55.8%
By crisis	44.2%

* For purposes of tabulation a return of temperature to normal in 36 hours or less was considered critical; more than this was considered defervescence by lysis.

*CHART I.



Complications. Most of the deaths were associated with some other condition. Of the 68 deaths occurring in this group, 42 were complicated by bronchopneumonia. Nephritis, hypertension, and arteriosclerosis were also frequent concomitant conditions, and were probably present before the appearance of encephalitis. Of the deaths occurring

* These curves are prepared from the data on 1091 cases of encephalitis reported to the St. Louis Health Division.

in the Isolation Hospital only about 10 per cent were without some complication diagnosed clinically.

Prognosis. The prognosis was much more favorable in younger individuals, as is shown by the fact that while 41.3 per cent of the cases reported in the epidemic were under 40 years of age, only 11.4 per cent of the deaths occurred in this group (Reports on 1091 cases to the St. Louis Health Division). The rise in the death rate with advancing age is graphically demonstrated when the curves of incidence and fatality are plotted on the same chart (Chart I).

Condition on Discharge. The condition of most patients on discharge from the hospital was surprisingly good except for some general weakness. Only 4.6 per cent showed any residua, and half of these consisted of such difficultly definable conditions as were recorded as mental or emotional abnormality. Only a detailed observation over a long period by the psychiatrists will make an evaluation of such findings possible. Photophobia was still present at discharge in two patients. Parkinson's syndrome appeared only one time. Lumbar puncture at the time of discharge, after three weeks isolation, showed a pleocytosis still present in several instances, although such examinations were not made routinely. No relapses or second attacks have been observed in this group of cases.

Treatment. Treatment was symptomatic. The most commonly employed measures were lumbar puncture for increasing headache or other evidence of advancing disease, and the intravenous administration of hypertonic glucose. A number of other therapeutic agents were employed, but none on a large enough scale for the results to be of significance.

Differential Diagnosis. Some cases of non-paralytic poliomyelitis probably cannot be differentiated with certainty from encephalitis. Poliomyelitis was present in St. Louis during the past summer, but the number of cases was not unusually large, so that mistakes in all probability were very few.

Tuberculous meningitis presented much more difficulty, but the onset is ordinarily more insidious, the spinal fluid sugar is usually markedly lowered, and the demonstration of tubercle bacilli would eliminate any doubt.

Follow-up. Plans have been made to follow the recovered cases for a period of two years. An examination of some of the patients 3 months after recovery has not shown any significant deviation from their condition at the time of discharge from the hospital.

Identity of the Disease. The relation of this illness to the lethargic encephalitis of v. Economo[3] naturally comes into question. The sudden, stormy onset, the acute and relatively short course, the predominance of signs of meningeal involvement, the low incidence of cranial nerve paralyses, and the rarity of residua seem to justify placing it in a separate clinical group. It is realized that cases indistinguishable from these have occurred in previous epidemics, but they were only a small fraction of the total number of cases. The clinical manifestations that we have observed, and the seasonal occurrence, correspond quite closely to encephalitis occurring in Japan[4] which has been classified as Type B.

Pathological changes occurring in the two types are quite similar, and consist of perivascular infiltration and some nerve cell destruction. Differentiation is probably more difficult for the pathologist than for the clinician.

Nevertheless, the clinical uniformity of such a large group of cases, which differ from most cases of lethargic encephalitis (v. Economo) requires that the possibility of different etiological agents be kept in mind.

Experimental

Early in the epidemic, research was centralized in the laboratories of the Departments of Medicine and Pathology of Washington University. This enabled experimental study of all cases in which collection of material would not interfere with work planned by the institution in which the patient was treated. Dr. Charles Armstrong, of the

National Institute of Health collaborated in this investigation throughout the course of the epidemic[5].

Many cultures of blood and spinal fluid were made with uniformly negative results, and animals of a number of species were inoculated with blood, spinal fluid, and filtered nasal washings from acute cases, and with brain tissue removed aseptically at autopsy. Shortly after beginning this work, some of the rhesus monkeys developed symptoms suggestive of encephalitis, and work with other animals at the time was to a large extent discontinued.

Emulsified brain tissue from fifteen cases was inoculated intracerebrally into rhesus monkeys, and in seven instances these animals developed fever, weakness, tremors and incoordination after an incubation period of from 8 to 21 days. These symptoms varied in degree, and sometimes were quite mild. The majority of animals showing symptoms were sacrificed, and passage in series through 5 monkeys was successful with four strains. Histological examination of the central nervous system showed changes consistent with human encephalitis, namely, perivascular cuffing and nerve cell degeneration. No bacteria were demonstrable.

Passage in monkeys was attended with considerable difficulty. Only about 40 per cent were susceptible, a large inoculum was necessary, and reinoculations were usually made after an interval of five days. At the time that this phase of the work was discontinued at Washington University and transferred to Dr. Armstrong at the National Institute of Health, one strain was still active in monkeys in our laboratory.

Among other animals, six horses and mules were used. One mule developed fever, lasting a few days, about ten days after inoculation but showed no other evidence of illness. Another mule, inoculated with monkey brain, developed fever and became obviously ill after about ten days. This animal was sacrificed, and histological examination of the brain revealed perivascular cuffing. Passage in this species was not successful, so the significance of the observation is open to question.

During the course of this work, glycerinated brain tissue was shipped to a number of laboratories. Dr. Webster[6], of the Rockefeller Institute, used a strain of mice, bred in his laboratory, which is highly susceptible to neurotropic viruses. In four out of eight attempts he was able to isolate a virus causing encephalitis in these mice. This virus was neutralized by sera from convalescents and was not neutralized by sera collected from normal individuals in New York.

Dr. Webster informed us of his findings, and we accordingly inoculated stock mice with brain tissue of monkeys showing signs of encephalitis. On first inoculation the takes were irregular, but on passage the virus became capable of causing the death of nearly 100 per cent of the animals. Three of the strains that were being passed in monkeys were established in mice. We have confirmed Dr. Webster's observation that the virus is neutralized by the serum of individuals convalescent from attacks of encephalitis during this epidemic.

This virus differs from that of herpes in a number of its characteristics, and at this point it should be stated that over thirty rabbits and eight cebus monkeys were inoculated with brain, blood, spinal fluid, or nasal washings without once encountering herpes virus. These results make it seem evident that herpes virus did not play a part in the St. Louis epidemic.

After intracerebral inoculation, the incubation period that we have observed in mice ordinarily varies between four and eight days, and is most commonly five or six days. At the expiration of this period the mice become hyperirritable and many have convulsive seizures. In a few hours they become quiescent, respiration is barely perceptible, and they will move only when strongly stimulated. Death follows shortly, and histological examination of the brain reveals perivascular cuffing and nerve cell degeneration.

The virus deteriorates fairly rapidly on standing, as is shown by the following experiment. An emulsion of fresh brain was diluted serially and inoculated immediately.

All of the mice given a dilution of 1-1,000,000 died. After standing for five hours at room temperature, only the dilutions up to 1-1,000 caused the death of all inoculated animals; and after 24 hours at room temperature this occurred only with the 1-10 dilution.

TABLE IV.

DETERIORATION OF VIRUS ON STANDING

	Immediate Inoculation	After 5 hours room temperature	After 24 hours room temperature
1-10	*3/3	3/3	3/3
1-100	3/3	3/3	2/3
1-1,000	3/3	3/3	1/3
1-10,000	3/3	1/3	
1-100,000	3/3		
1-1,000,000	3/3		

* These fractions indicate the number of mice dying over the number inoculated.

There is a gradual deterioration in 50 per cent glycerine in the ice box, but after 5 weeks we have demonstrated active virus, although only a few of the inoculated animals have succumbed, and the incubation period was prolonged.

The frequency with which this virus has been encountered, and its neutralization by the serum of patients convalescent from encephalitis lead one to think that it was of etiological significance in the St. Louis epidemic.

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THE THOMAS W. SALMON MEMORIAL COMMITTEE REPORT AND PRESENTATION OF PORTRAIT OF THE LATE DR. THOMAS W. SALMON*

Mr. President, Fellows and Members of the Academy:

I appreciate the honor of having been requested by your President to appear upon the program of this Annual Meeting. In behalf of the Thomas W. Salmon Memorial Committee of the Academy, I wish briefly to account for our stewardship.

In keeping with the obligations assumed by this Committee, as agent for the Academy, the fields of psychiatry and mental hygiene have been surveyed in this country and abroad and the names of twenty-seven leaders in psychiatry, neurology, mental hygiene, psychology and the social sciences have been before the Committee for more than a year as possible recipients of the Salmon Lectureship award. The recent and remote contributions of these scientists have been made a matter of record and in the archives of the Committee future accomplishments will be recorded.

It is a great pleasure to be able to advise the fellows of the Academy of the unanimous selection of Dr. C. Macfie Campbell, as the Thomas W. Salmon Memorial Lecturer for the year 1934. Dr. Campbell, Professor of Psychiatry at Harvard University since 1920, has been an active participant in all the leading movements for the advancement of psychiatry. He was for a number of years President of the Massachusetts Mental Hygiene Society. He delivered the Shattuck Lecture in 1924 on "Psychiatry and the Practice of Medicine," the Gehrmann Lectures in Hygiene at the University of Illinois, in 1932, on "The Schizophrenia Problem"; and the Lowell Lectures in Boston, in 1932, on "Human Personality and the Environment." His experience in directing a hospital which deals with a wide variety of social problems associated with psychiatric conditions and his eminence in the psychiatric world are so well known that it is unnecessary to review in detail his many contributions.

* Read at the Annual Meeting of the Council of The New York Academy of Medicine, January 4, 1934.

The Salmon Memorial Lectures will be given here on April 13, 20 and 27, 1934.

Not only has the Committee been charged with the responsibility of selecting the Salmon lecturer, but upon it has devolved the task of stimulating advance in psychiatry and associated fields within the resources at its command. To this end eighteen applications for financial assistance of research projects have been reviewed by the Committee. The large number of applications for aid necessitated the formulation of a policy which favors subsidizing research which can be made effective by a grant of a comparatively modest amount.

The following projects were chosen for subsidies by the Committee:

Miss Muriel T. Bashlow, Judge Baker Foundation—for studies on "Psychometric results of clinical psychotherapy in cases of emotional blocking among juveniles."

Dr. Clarence O. Cheney, New York Psychiatric Institute—for "Endocrinological studies in psychiatric patients."

Dr. Franklin G. Ebaugh, Colorado Psychopathic Hospital, Denver—for "Studies on treatment of epilepsy with Emmenin (the name applied by Professor Collip of McGill University to a hormone he has isolated from human placentas)."

Dr. Norman Fenton, Bureau of Juvenile Research, California—for "A study of the mental and social traits of four hundred boys in a State correctional school and the relationship of these traits to later behavior on placement."

Dr. John Levy, New York—for "An experimental study of therapeutic approaches to enuresis."

Dr. Jacob Kasanin, Clinical Director, State Hospital for Mental Diseases, Howard, Rhode Island—for the purchase of an oscillometer for "Investigation of the peripheral circulation in schizophrenia."

Dr. James L. McCartney, Director, Classification Clinic at Elmira, New York—for a "Classification of Prisoners."

Dr. Lloyd H. Ziegler, Professor of Psychiatry and Neurology at Albany Medical College—for a "Study of psychopathic affects and their relation to the surface temperature of the body."

The Editorial Board of the Archives of Neurology and Psychiatry—for the reprinting and distribution of certain articles dealing with the training of the neurologist and psychiatrist.

The Committee will welcome suggestions and information in regard to problems presenting new and promising contributions which may be furthered by these modest grants now available.

A further responsibility has been entrusted to me by the Committee, and one regarding which I have considerable sentiment. I am sure that each member of the Committee, who was personally attached to Dr. Salmon, would have been pleased to have had this duty entrusted to him, but through the generosity of the members, I have been selected to present to the Academy this portrait of Dr. Salmon. To all of us he is not only one of the great leaders of psychiatry, but one of the great men in medicine of our day. I have not altogether a cordial feeling about using the word "memorial" in connection with one whose leadership unquestionably continues. It suggests somewhat the termination of a man's life work. So it is that this portrait is presented to the Academy not as part of a memorial to Dr. Salmon, but as a symbol of a living movement.

DR. C. C. BURLINGAME, *Chairman*

DR. GEORGE H. KIRBY
DR. ADOLF MEYER
DR. FREDERICK TILNEY
DR. WILLIAM L. RUSSELL
DR. E. G. ZABRISKIE
DR. BERNARD SACHS